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UNITED STATES PATENT APPLICATION

FOR

TRICYCLIC AMINOCYANOPYRIDINE INHIBITORS OF MITOGEN ACTIVATED PROTEIN KINASE-ACTIVATED PROTEIN KINASE-2

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TRICYCLIC AMINOCYANOPYRIDINE INHIBITORS OF MITOGEN ACTIVATED PROTEIN KINASE-ACTIVATED PROTEIN KINASE-2

CROSS REFERENCE TO RELATED PATENTS AND PATENT APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/432,844, filed December 12, 2002, which is incorporated by reference herein in its entirety. This application is related to commonly assigned and copending applications having the titles "Method of using aminocyanopyridine compounds as mitogen activated protein kinase-activated protein kinase-2 inhibitors" (and having Provisional Application Serial No. 60/432,807), and "Method of making tricyclic aminocyanopyridine compounds" (and having Provisional Application Serial No. 60/432,783), each of which was filed on the same date as the present application.

BACKGROUND OF THE INVENTION

(1) Field of the Invention:

[0002] The present invention relates to aminocyanopyridine compounds, and in particular, to tricyclic aminocyanopyridine compounds which inhibit mitogen-activated protein kinase-activated protein kinase-2 (MAPKAP kinase-2, or MK-2), and compositions containing those aminocyanopyridine compounds.

(2) Description of the Related Art:

[0003] Mitogen-activated protein kinases (MAPKs) are members of conserved signal transduction pathways that activate transcription factors, translation factors and other target molecules in response to a variety of extracellular signals. MAPKs are activated by phosphorylation at a dual phosphorylation motif with the sequence Thr-X-Tyr by mitogen-activated protein kinase kinases (MAPKKs). In higher eukaryotes, the physiological role of MAPK signaling has been correlated with cellular events such as proliferation, oncogenesis, development and differentiation. Accordingly, the ability to regulate signal transduction via these pathways could lead to

the development of treatments and preventive therapies for human diseases associated with MAPK signaling, such as inflammatory diseases, autoimmune diseases and cancer.

[0004] In mammalian cells, three parallel MAPK pathways have been described. The best characterized pathway leads to the activation of the extracellular-signal-regulated kinase (ERK). Less well understood are the signal transduction pathways leading to the activation of the cJun N-terminal kinase (JNK) and the p38 MAPK. See, *e.g.*, Davis, *Trends Biochem. Sci. 19*:470-473 (1994); Cano, *et al., Trends Biochem. Sci. 20*:117-122(1995).

[0005] The p38 MAPK pathway is potentially activated by a wide variety of stresses and cellular insults. These stresses and cellular insults include heat shock, UV irradiation, inflammatory cytokines (such as TNF and IL-1), tunicamycin, chemotherapeutic drugs (*i.e.*, cisplatinum), anisomycin, sorbitol/hyperosmolarity, gamma irradiation, sodium arsenite, and ischaemia. See, Ono, K., *et al, Cellular Signalling 12*, 1 - 13 (2000). Activation of the p38 pathway is involved in (1) production of proinflammatory cytokines, such as TNF-α; (2) induction of enzymes, such as Cox-2; (3) expression of an intracellular enzyme, such as iNOS, which plays an important role in the regulation of oxidation; (4) induction of adherent proteins, such as VCAM-1 and many other inflammatory-related molecules. Furthermore, the p38 pathway functions as a regulator in the proliferation and differentiation of cells of the immune system. See, Ono, K., *et al., Id.* at 7.

[0006] The p38 kinase is an upstream kinase of mitogen-activated protein kinase-activated protein kinase-2 (MAPKAP kinase-2 or MK-2). (See, Freshney, N. W.; *et al., J. Cell, 78*:1039-1049 (1994)). MK-2 is a protein that appears to be predominantly regulated by p38 in cells. Indeed, MK-2 was the first substrate of p38α to be identified. For example, *in vitro* phosphorylation of MK-2 by p38α activates MK-2. The substrates that MK-2 acts upon, in turn, include heat shock protein 27, lymphocyte-specific protein 1 (LAP1), cAMP response element-binding

protein (CREB), ATF1, serum response factor (SRF), and tyrosine hydroxylase. The substrate of MK-2 that has been best characterized is small heat shock protein 27 (hsp27).

[0007] The role of the p38 pathway in inflammatory-related diseases has been studied in several animal models. The pyridinyl imidazole compound SB203580 has been shown to be a specific inhibitor of p38 *in vivo,* and also has been shown to inhibit activation of MK-2, (See, Rouse, J., *et al, Cell, 78*:1027-1037 (1994); Cuenda, A., *et al, Biochem. J., 333*:11-15 (1998)), as well as a MAP kinase homologue termed reactivating kinase (RK). (See, Cuenda, A., *et al., FEBS Lett., 364(2)*:229 - 233 (1995)). Inhibition of p38 by SB203580 can reduce mortality in a murine model of endotoxin-induced shock and inhibit the development of mouse collagen-induced arthritis and rat adjuvant arthritis. See, *e.g.*, Badger, A. M., *et al., J. Pharmacol Exp. Ther., 279*:1453 - 1461 (1996). Another p38 inhibitor that has been utilized in an animal model that is believed to be more potent than SB203580 in its inhibitory effect on p38 is SB 220025. A recent animal study has demonstrated that SB 220025 caused a significant dose-dependent decrease in vascular density of granulomas in laboratory rats. (See, Jackson, J. R., *et al, J. Pharmacol. Exp. Ther., 284*:687 - 692 (1998)). The results of these animal studies indicated that p38, or the components of the p38 pathway, can be useful therapeutic targets for the prevention or treatment of inflammatory disease.

[0008] Due to its integral role in the p38 signaling pathway, MK-2 has been used as a monitor for measuring the level of activation in the pathway. Because of its downstream location in the pathway, relative to p38, MK-2 has been measured as a more convenient, albeit indirect, method of assessing p38 activation. However, so far, research efforts exploring therapeutic strategies associated with the modulation of this pathway have focused mainly on the inhibition of p38 kinase.

[0009] Several compounds that inhibit the activity of p38 kinase have been described in U.S. Patent Nos. 6,046,208, 6,251,914, and 6,335,340.

These compounds have been suggested to be useful for the treatment of CSBP/RK/p38 kinase mediated disease. Commercial efforts to apply p38 inhibitors have centered around two p38 inhibitors, the pyridinylimidazole inhibitor SKF 86002, and the 2,4,5 triaryl imidazole inhibitor SB203580. See, Lee, J. C., *et al, Immunopharmacology 47,* 185-192 (2000). Compounds possessing a similar structure have also been investigated as potential p38 inhibitors. Indeed, p38 MSP kinase's role in various disease states has been elucidated through the use of inhibitors.

[00010] Kotlyarov, A. *et al,* in *Nat. Cell Biol., 1(2)*:94 - 97 (1999) introduced a targeted mutation into a mouse MK-2 gene, resulting in MK-2-deficient mice. It was shown that mice lacking MK-2 possessed increased stress resistance and survived LPS-induced endotoxic shock better than MK-2$^+$ mice. The authors concluded that MK-2 was an essential component in the inflammatory response that regulates biosynthesis of TNFα at a post-transcriptional level. More recently, Lehner, M.D., *et al,* in *J. Immunol., 168(9)*:4667-4673 (2002), reported that MK-2-deficient mice showed increased susceptibility to *Listeria monocytogenes* infection, and concluded that MK-2 had an essential role in host defense against intracellular bacteria, probably via regulation of TNF and IFN-gamma production required for activation of antibacterial effector mechanisms.

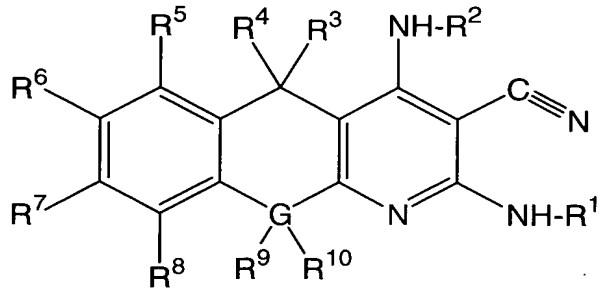
[00011] The location of MK-2 in the p38 signaling pathway at a point that is downstream of p38 offers the potential that MK-2 could act as a focal point for modulating the pathway without affecting as many substrates as would the regulation of an enzyme further upstream in the signaling cascade -- such as p38 MAP kinase.

[00012] Accordingly, it would be useful to provide compounds that could serve to modulate the activity of MK-2 -- in particular, to act as inhibitors of MK-2 activity. Such compounds would be useful for the provision of benefits similar to p38 MAP kinase inhibitors, which benefits include the prevention and treatment of diseases and disorders that are mediated by TNFα. It would be even more useful to provide MK-2 inhibitors having

improved potency and reduced undesirable side effects, relative to p38 inhibitors.

SUMMARY OF THE INVENTION

[00013] Briefly, therefore the present invention is directed to a novel aminocyanopyridine compound having the structure:



wherein:

R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 each is independently selected from the group consisting of

hydrogen, hydroxy, amino, halo, nitro,

branched or unbranched C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, hydroxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkenoxy,

branched or unbranched amino C_1-C_6 alkyl, diamino C_2-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, C_1-C_6 alkylamino, di-(C_1-C_6 alkyl)amino, C_1-C_4 alkoxyarylamino, C_1-C_4 alkoxyalkylamino, amino C_1-C_6 alkoxy, di-(C_1-C_4 alkylamino, C_2-C_6 alkoxy, di-(C_1-C_6 alkyl)amino C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkoxy, halo C_1-C_6 alkoxy, dihalo C_1-C_6 alkoxy, trihalo C_1-C_6 alkoxy, cyano C_1-C_6 alkyl, dicyano C_1-C_6 alkyl, cyano C_1-C_6 alkoxy, dicyano C_1-C_6 alkoxy, carbamyl C_1-C_4 alkoxy, heterocyclyl C_1-C_4 alkoxy, heteroaryl C_1-C_4 alkoxy, sulfo, sulfamyl, C_1-C_4 alkylaminosulfonyl, hydroxy C_1-C_4 alkylaminosulfonyl, di-(C_1-C_4 alkyl)aminosulfonyl, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylsulfinyl,

aryl, aryl C_1-C_6 alkyl, heterocyclyl C_1-C_6 alkyl, heteroaryl C_1-C_6 alkyl, heterocyclyl C_1-C_6 alkoxy, heteroaryl C_1-C_6 alkoxy, aryl C_1-C_6 alkoxy, where the aryl ring can be substituted or unsubstituted, and, if substituted,

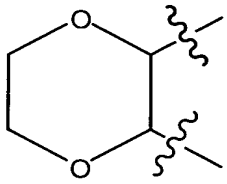
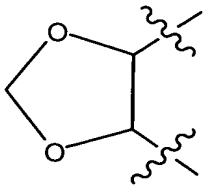
the substituent group is selected from one or more of the group consisting of C_1-C_6 alkyl, halo, amino, and C_1-C_6 alkoxy,

substituted or unsubstituted C_3-C_6 cyclyl, C_3-C_6 heterocyclyl, and, if substituted, the substituent group is selected from one or more of the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, amino, and where the C_3-C_6 heterocyclyl ring contains O, S, or N,

branched or unbranched C_1-C_6 alkoxycarbonyl C_1-C_6 alkoxy, and

carboxy, carboxy C_1-C_6 alkoxy, carboxy C_1-C_6 alkyl, hydroxy C_1-C_4 alkoxycarbonyl, C_1-C_4 alkoxycarbonyl,

where R^6 and R^7 are such that they optionally join to form a ring system of the type selected from

 , and  ;

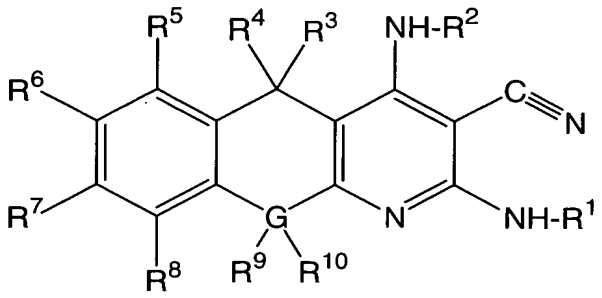
G is selected from the group consisting of oxygen, sulfur, and nitrogen;

when G is oxygen, R^9 and R^{10} are absent;

when G is sulfur, each of R^9 and R^{10} is optionally absent, or is oxo;

when G is nitrogen, R^4 is -H, R^9 is absent, and R^{10} is C_1-C_4-alkyl.

[00014] The present invention is also directed to a novel pharmaceutical composition comprising a pharmaceutically acceptable carrier and an aminocyanopyridine MK-2 inhibiting compound having the structure:



wherein:

R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 each is independently selected from the group consisting of

hydrogen, hydroxy, amino, halo, nitro,

branched or unbranched C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, hydroxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkenoxy,

branched or unbranched amino C_1-C_6 alkyl, diamino C_2-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, C_1-C_6 alkylamino, di-(C_1-C_6 alkyl)amino, C_1-C_4 alkoxyarylamino, C_1-C_4 alkoxyalkylamino, amino C_1-C_6 alkoxy, di-(C_1-C_4 alkylamino, C_2-C_6 alkoxy, di-(C_1-C_6 alkyl)amino C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkoxy, halo C_1-C_6 alkoxy, dihalo C_1-C_6 alkoxy, trihalo C_1-C_6 alkoxy, cyano C_1-C_6 alkyl, dicyano C_1-C_6 alkyl, cyano C_1-C_6 alkoxy, dicyano C_1-C_6 alkoxy, carbamyl C_1-C_4 alkoxy, heterocyclyl C_1-C_4 alkoxy, heteroaryl C_1-C_4 alkoxy, sulfo, sulfamyl, C_1-C_4 alkylaminosulfonyl, hydroxy C_1-C_4 alkylaminosulfonyl, di-(C_1-C_4 alkyl)aminosulfonyl, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylsulfinyl,

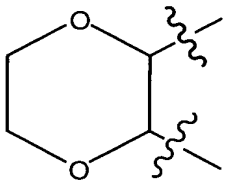
aryl, aryl C_1-C_6 alkyl, heterocyclyl C_1-C_6 alkyl, heteroaryl C_1-C_6 alkyl, heterocyclyl C_1-C_6 alkoxy, heteroaryl C_1-C_6 alkoxy, aryl C_1-C_6 alkoxy, where the aryl ring can be substituted or unsubstituted, and, if substituted, the substituent group is selected from one or more of the group consisting of C_1-C_6 alkyl, halo, amino, and C_1-C_6 alkoxy,

substituted or unsubstituted C_3-C_6 cyclyl, C_3-C_6 heterocyclyl, and, if substituted, the substituent group is selected from one or more of the

group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, amino, and where the C_3-C_6 heterocyclyl ring contains O, S, or N,

branched or unbranched C_1-C_6 alkoxycarbonyl C_1-C_6 alkoxy, and carboxy, carboxy C_1-C_6 alkoxy, carboxy C_1-C_6 alkyl, hydroxy C_1-C_4 alkoxycarbonyl, C_1-C_4 alkoxycarbonyl,

where R^6 and R^7 are such that they optionally join to form a ring system of the type selected from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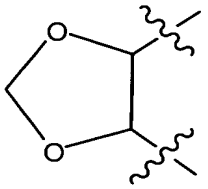

;

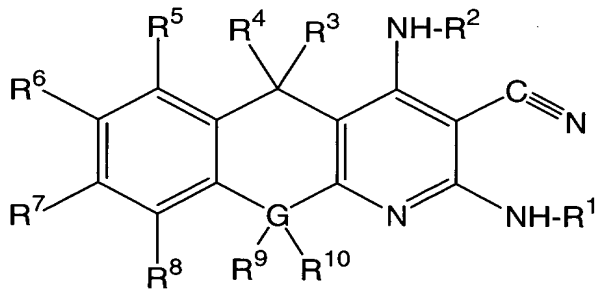
G is selected from the group consisting of oxygen, sulfur, and nitrogen;

when G is oxygen, R^9 and R^{10} are absent;

when G is sulfur, each of R^9 and R^{10} is optionally absent, or is oxo;

when G is nitrogen, R^9 is absent, and R^{10} is C_1-C_4-alkyl.

[00015] The present invention is also directed to a novel kit comprising a dosage form containing an aminocyanopyridine MK-2 inhibiting compound having the structure:



wherein:

R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 each is independently selected from the group consisting of

hydrogen, hydroxy, amino, halo, nitro,

branched or unbranched C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, hydroxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkenoxy,

branched or unbranched amino C_1-C_6 alkyl, diamino C_2-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, C_1-C_6 alkylamino, di-(C_1-C_6 alkyl)amino, C_1-C_4 alkoxyarylamino, C_1-C_4 alkoxyalkylamino, amino C_1-C_6 alkoxy, di-(C_1-C_4 alkylamino, C_2-C_6 alkoxy, di-(C_1-C_6 alkyl)amino C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkoxy, halo C_1-C_6 alkoxy, dihalo C_1-C_6 alkoxy, trihalo C_1-C_6 alkoxy, cyano C_1-C_6 alkyl, dicyano C_1-C_6 alkyl, cyano C_1-C_6 alkoxy, dicyano C_1-C_6 alkoxy, carbamyl C_1-C_4 alkoxy, heterocyclyl C_1-C_4 alkoxy, heteroaryl C_1-C_4 alkoxy, sulfo, sulfamyl, C_1-C_4 alkylaminosulfonyl, hydroxy C_1-C_4 alkylaminosulfonyl, di-(C_1-C_4 alkyl)aminosulfonyl, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylsulfinyl,

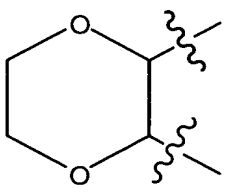
aryl, aryl C_1-C_6 alkyl, heterocyclyl C_1-C_6 alkyl, heteroaryl C_1-C_6 alkyl, heterocyclyl C_1-C_6 alkoxy, heteroaryl C_1-C_6 alkoxy, aryl C_1-C_6 alkoxy, where the aryl ring can be substituted or unsubstituted, and, if substituted, the substituent group is selected from one or more of the group consisting of C_1-C_6 alkyl, halo, amino, and C_1-C_6 alkoxy,

substituted or unsubstituted C_3-C_6 cyclyl, C_3-C_6 heterocyclyl, and, if substituted, the substituent group is selected from one or more of the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, amino, and where the C_3-C_6 heterocyclyl ring contains O, S, or N,

branched or unbranched C_1-C_6 alkoxycarbonyl C_1-C_6 alkoxy, and

carboxy, carboxy C_1-C_6 alkoxy, carboxy C_1-C_6 alkyl, hydroxy C_1-C_4 alkoxycarbonyl, C_1-C_4 alkoxycarbonyl,

where R^6 and R^7 are such that they optionally join to form a ring system of the type selected from



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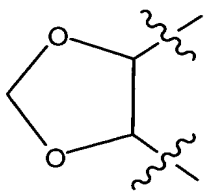


;

G is selected from the group consisting of oxygen, sulfur, and nitrogen;

when G is oxygen, R^9 and R^{10} are absent;

when G is sulfur, each of R^9 and R^{10} is optionally absent, or is oxo;

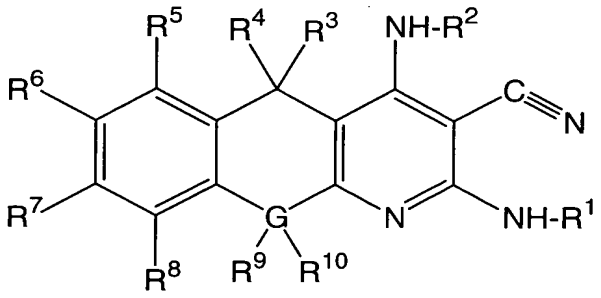
when G is nitrogen, R^9 is absent, and R^{10} is C_1-C_4-alkyl.

[00016] Among the several advantages found to be achieved by the present invention, therefore, may be noted the provision of a compound that could serve to modulate the activity of MK-2 -- in particular, to inhibit MK-2 activity, and the provision of a compound that is useful for the prevention and treatment of diseases and disorders that are mediated by TNFα.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[00017] In accordance with the present invention, it has been discovered that certain aminocyanopyridine compounds can inhibit the activity of MAPKAP kinase-2. Many of these compounds exhibit their inhibitory effect at low concentrations -- having *in vitro* MK-2 inhibition IC_{50} values of under 1.0 μM, and with some having IC_{50} values of under about 0.5 μM, and even as low as about 0.2 μM. Accordingly, these compounds can be potent and effective drugs for use in methods to prevent or treat diseases and disorders that are mediated by TNFα. For example, they can be used for the prevention or treatment of arthritis.

[00018] Aminocyanopyridine compounds that are useful in the present method include those aminocyanopyridine compounds having the structure shown in formula I:



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wherein:

R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 each is independently selected from the group consisting of

hydrogen, hydroxy, amino, halo, nitro,

branched or unbranched C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, hydroxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkenoxy,

branched or unbranched amino C_1-C_6 alkyl, diamino C_2-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, C_1-C_6 alkylamino, di-(C_1-C_6 alkyl)amino, C_1-C_4 alkoxyarylamino, C_1-C_4 alkoxyalkylamino, amino C_1-C_6 alkoxy, di-(C_1-C_4 alkylamino, C_2-C_6 alkoxy, di-(C_1-C_6 alkyl)amino C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkoxy, halo C_1-C_6 alkoxy, dihalo C_1-C_6 alkoxy, trihalo C_1-C_6 alkoxy, cyano C_1-C_6 alkyl, dicyano C_1-C_6 alkyl, cyano C_1-C_6 alkoxy, dicyano C_1-C_6 alkoxy, carbamyl C_1-C_4 alkoxy, heterocyclyl C_1-C_4 alkoxy, heteroaryl C_1-C_4 alkoxy, sulfo, sulfamyl, C_1-C_4 alkylaminosulfonyl, hydroxy C_1-C_4 alkylaminosulfonyl, di-(C_1-C_4 alkyl)aminosulfonyl, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylsulfinyl,

aryl, aryl C_1-C_6 alkyl, heterocyclyl C_1-C_6 alkyl, heteroaryl C_1-C_6 alkyl, heterocyclyl C_1-C_6 alkoxy, heteroaryl C_1-C_6 alkoxy, aryl C_1-C_6 alkoxy, where the aryl ring can be substituted or unsubstituted, and, if substituted, the substituent group is selected from one or more of the group consisting of C_1-C_6 alkyl, halo, amino, and C_1-C_6 alkoxy,

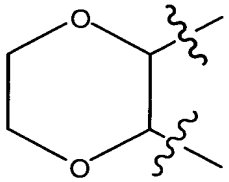
substituted or unsubstituted C_3-C_6 cyclyl, C_3-C_6 heterocyclyl, and, if substituted, the substituent group is selected from one or more of the

group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, amino, and where the C_3-C_6 heterocyclyl ring contains O, S, or N,

branched or unbranched C_1-C_6 alkoxycarbonyl C_1-C_6 alkoxy, and

carboxy, carboxy C_1-C_6 alkoxy, carboxy C_1-C_6 alkyl, hydroxy C_1-C_4 alkoxycarbonyl, C_1-C_4 alkoxycarbonyl,

where R^6 and R^7 are such that they optionally join to form a ring system of the type selected from



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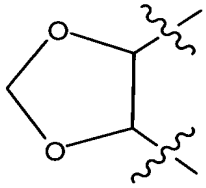


.

[00019] As shown above, ring substituent groups that join to form additional ring structures adjacent the substituted ring can be described with reference to chemical formulas that show wavy lines to indicate that a partial molecule is shown. In these formulas, the wavy lines cut through the ring to which the substituents are joined (in this case, the phenyl ring of formula I), rather than across the bond joining the substituent group to the ring. Accordingly, the partial ring that is shown is the ring to which the substituent groups are shown as being bonded in the general formula.

[00020] G is selected from the group consisting of oxygen, sulfur, and nitrogen;

when G is oxygen, R^9 and R^{10} are absent;

when G is sulfur, each of R^9 and R^{10} is optionally absent, or is oxo;

when G is nitrogen, R^4 is -H, R^9 is absent, and R^{10} is C_1-C_4-alkyl.

[00021] In preferred embodiments, R^6 is other than cyano.

[00022] As used herein, the term "alkyl", alone or in combination, means an acyclic alkyl radical, linear or branched, which, unless otherwise noted, preferably contains from 1 to about 10 carbon atoms and more preferably contains from 1 to about 6 carbon atoms. "Alkyl" also encompasses cyclic alkyl radicals containing from 3 to about 7 carbon atoms, preferably from 3 to 5 carbon atoms. The alkyl radicals can be

optionally substituted with groups as defined below. Examples of such alkyl radicals include methyl, ethyl, chloroethyl, hydroxyethyl, n-propyl, isopropyl, n-butyl, cyanobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, aminopentyl, iso-amyl, hexyl, octyl, and the like.

[00023] The term "alkenyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains at least one double bond. Unless otherwise noted, such radicals preferably contain from 2 to about 6 carbon atoms, preferably from 2 to about 4 carbon atoms, more preferably from 2 to about 3 carbon atoms. The alkenyl radicals may be optionally substituted with groups as defined below. Examples of suitable alkenyl radicals include propenyl, 2-chloropropylenyl, buten-1yl, isobutenyl, penten-1yl, 2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, 3-hydroxyhexen-1-yl, hepten-1-yl, octen-1-yl, and the like.

[00024] The term "alkynyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains one or more triple bonds, such radicals preferably containing 2 to about 6 carbon atoms, more preferably from 2 to about 3 carbon atoms. The alkynyl radicals may be optionally substituted with groups as described below. Examples of suitable alkynyl radicals include ethynyl, proynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyl-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals, and the like.

[00025] The term "alkoxy" includes linear or branched oxy-containing radicals, each of which has, unless otherwise noted, alkyl portions of 1 to about 6 carbon atoms, preferably 1 to about 4 carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, isobutoxy radicals, and the like.

[00026] The term "alkoxyalkyl" also embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. Examples of such radicals include methoxyalkyls, ethoxyalkyls, propoxyalkyls, isopropoxyalkyls, butoxyalkyls, tert-butoxyalkyls, and the like. The "alkoxy" radicals may be

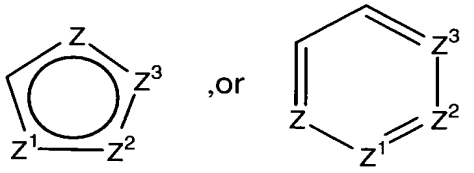
further substituted with one or more halo atoms, such as fluoro, chloro, or bromo, to provide "haloalkoxy" radicals. Examples of such radicals includ fluoromethoxy, chloromethoxy, trifluoromethoxy, difluoromethoxy, trifluoroethoxy, fluoroethoxy, tetrafluoroethoxy, pentafluoroethoxy, fluoropropoxy, and the like.

[00027] The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, preferably, unless otherwise noted, of from 1 to about 6 carbon atoms, attached to a divalent sulfur atom. An example of "lower alkylthio", is methylthio (CH_3-S-).

[00028] The term "alkylthioalkyl" embraces alkylthio radicals, attached to an alkyl group. An example of such radicals is methylthiomethyl.

[00029] The term "halo" means radicals comprising halogens, such as fluorine, chlorine, bromine, or iodine.

[00030] The term "heterocyclyl" means a saturated or unsaturated mono- or multi-ring carbocycle wherein one or more carbon atoms is replaced by N, S, P, or O. This includes, for example, structures such as:



where Z, Z^1, Z^2, or Z^3 is C, S, P, O, or N, with the proviso that one of Z, Z^1, Z^2, or Z^3 is other than carbon, but is not O or S when attached to another Z atom by a double bond or when attached to another O or S atom. Furthermore, the optional substituents are understood to be attached to Z, Z^1, Z^2, or Z^3 only when each is C. The term "heterocycle" also includes fully saturated ring structures, such as piperazinyl, dioxanyl, tetrahydrofuranyl, oxiranyl, aziridinyl, morpholinyl, pyrrolidinyl, piperidinyl, thiazolidinyl, and others.

[00031] The term "heteroaryl" means a fully unsaturated heterocycle, which can include, but is not limited to, furyl, thenyl, pyrryl, imidazolyl,

pyrazolyl, pyridyl, thiazolyl, quinolinyl, isoquinolinyl, benzothienyl, and indolyl.

[00032] In either, "heterocyclyl" or "heteroaryl", the point of attachment to the molecule of interest can be at the heteroatom or elsewhere within the ring.

[00033] The term "cycloalkyl" means a mono- or multi-ringed carbocycle wherein each ring contains three to about seven carbon atoms, preferably three to about six carbon atoms, and more preferably three to about five carbon atoms. Examples include radicals, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloalkenyl, and cycloheptyl. The term "cycloalkyl" additionally encompasses spiro systems wherein the cycloalkyl ring has a carbon ring atom in common with the seven-membered heterocyclic ring of the benzothiepine.

[00034] The term "oxo" means a doubly-bonded oxygen.

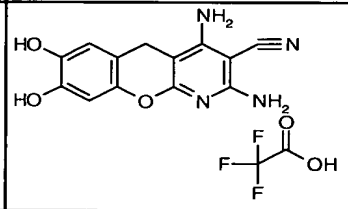
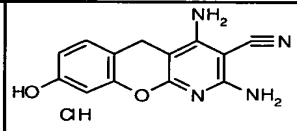
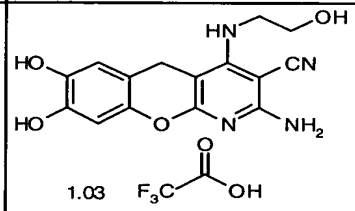
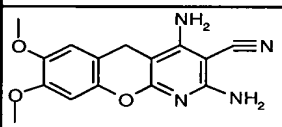
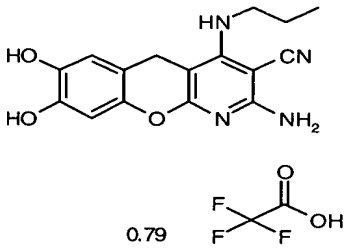
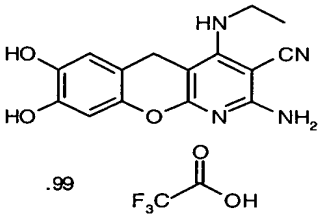
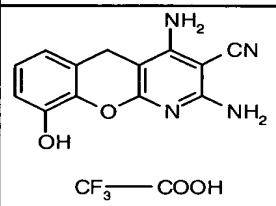
[00035] The term "aryl" means a fully unsaturated mono- or multi-ring carbocycle, including, but not limited to, substituted or unsubstituted phenyl, naphthyl, or anthracenyl.

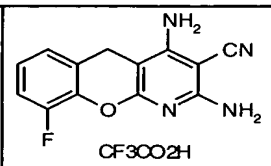
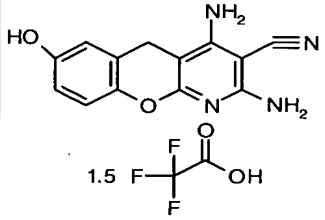
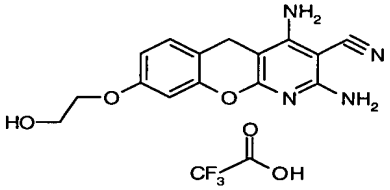
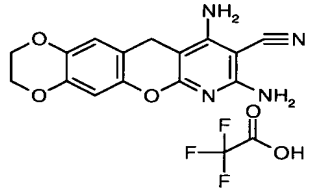
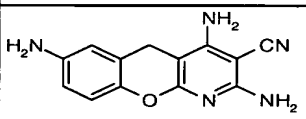
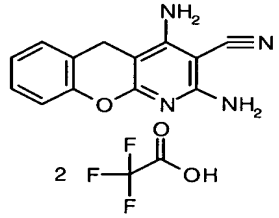
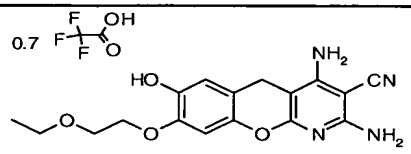
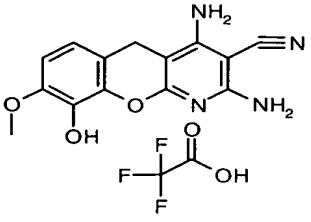
[00036] The present aminocyanopyridine compounds inhibit the activity of the MK-2 enzyme. When it is said that a subject compound inhibits MK-2, it is meant that the MK-2 enzymatic activity is lower in the presence of the compound than it is under the same conditions in the absence of such compound. One method of expressing the potency of a compound as an MK-2 inhibitor is to measure the "IC_{50}" value of the compound. The IC_{50} value of an MK-2 inhibitor is the concentration of the compound that is required to decrease the MK-2 enzymatic activity by one-half. Accordingly, a compound having a lower IC_{50} value is considered to be a more potent inhibitor than a compound having a higher IC_{50} value. As used herein, aminocyanopyridine compounds that inhibit MK-2 can be referred to as aminocyanopyridine MK-2 inhibitors, or aminocyanopyridine MK-2 inhibiting compounds or MK-2 inhibiting agents.

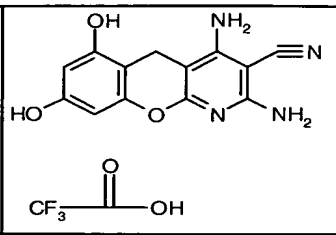
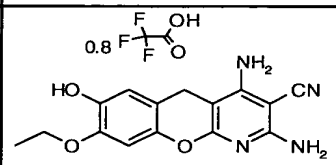
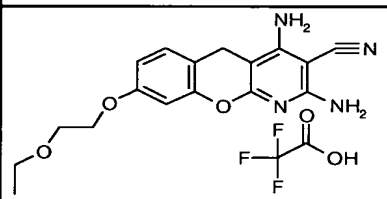
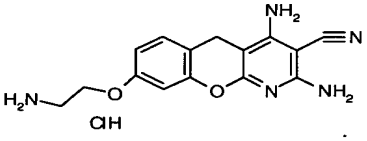
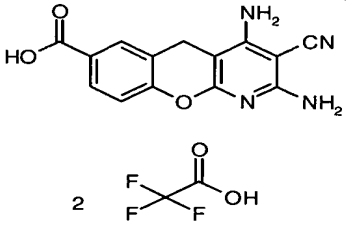
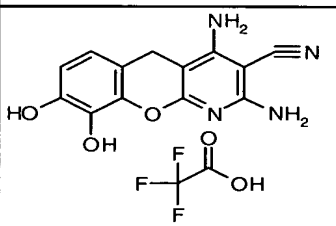
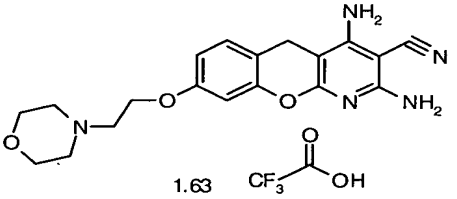
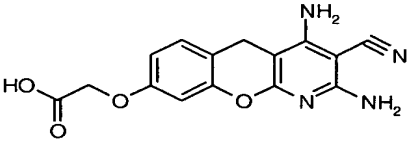
[00037] The tricyclic aminocyanopyridine compounds that are useful in the present invention include benzonapthyridines, pyridochromanes, and pyridothiochromanes.

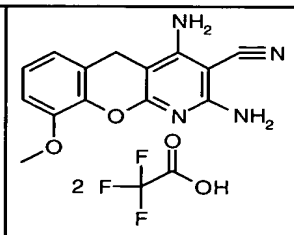
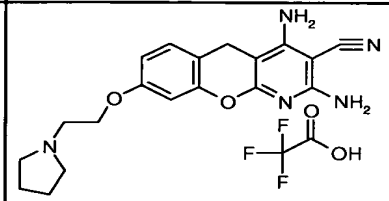
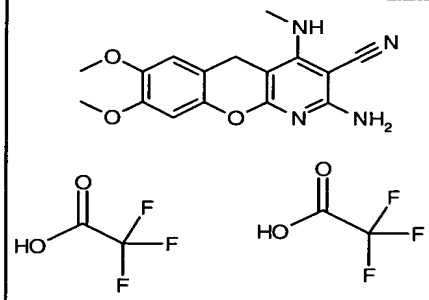
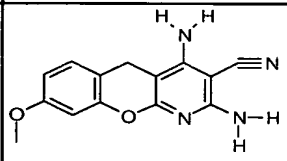
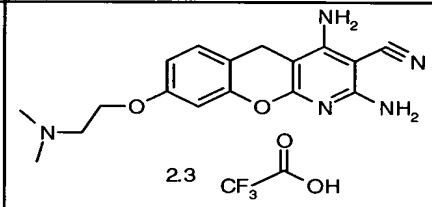
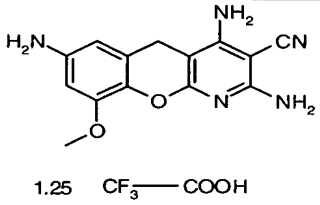
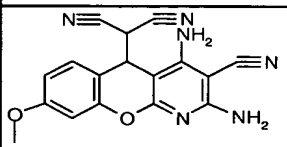
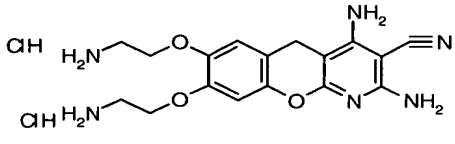
[00038] Examples of tricyclic aminocyanopyridine compounds that are useful as MK-2 inhibitors in the present method are shown in Table I.

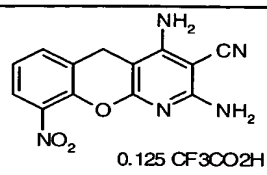
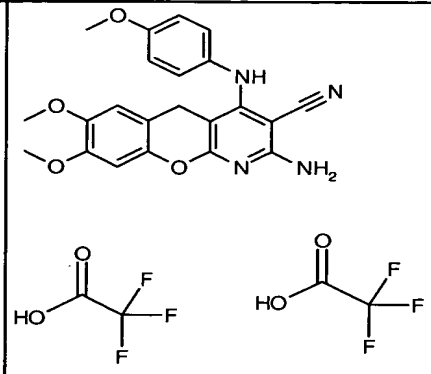
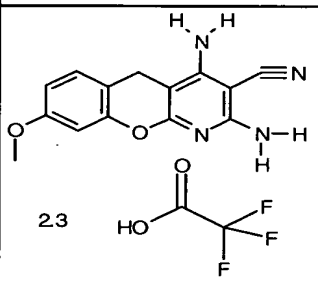
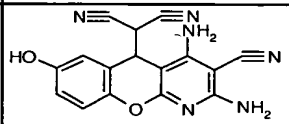
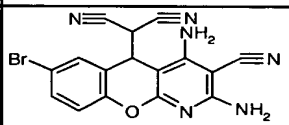
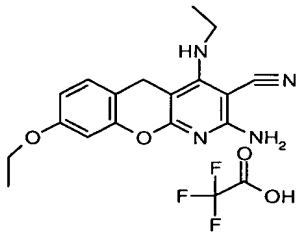
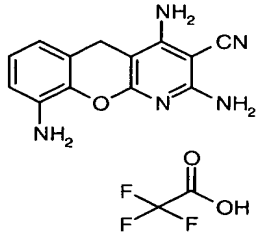
Table I: Aminocyanopyridine MK-2 Inhibitors

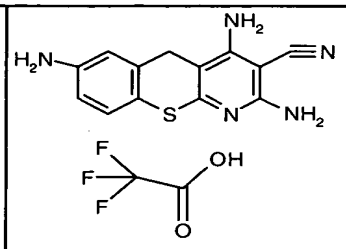
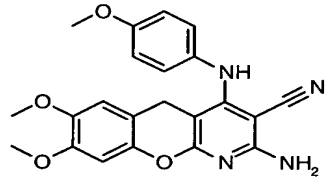
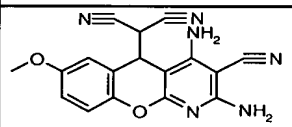
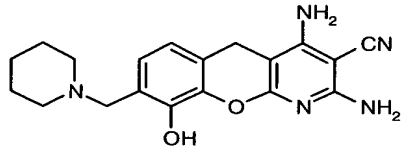
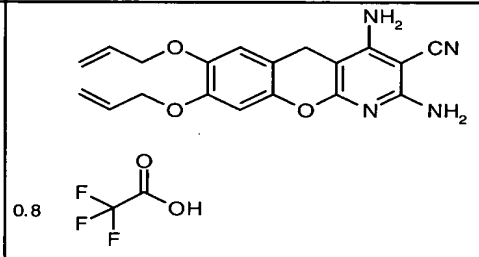
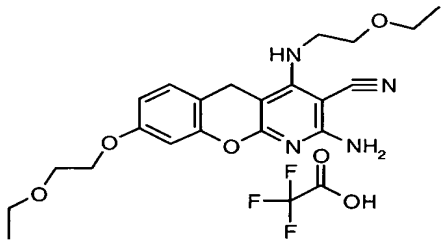
No.	Structur [a]	Comp und Name(s)[b]	MK-2 Avg. IC50 (uM)
1		2,4-diamino-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.125
2		2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile hydrochloride	0.187
3		2-amino-7,8-dihydroxy-4-[(2-hydroxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.237
4		2,4-diamino-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	0.335
5		2-amino-7,8-dihydroxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.403
6		2-amino-4-(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.419
7		2,4-diamino-9-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.459

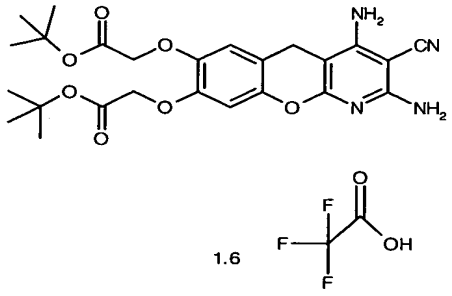
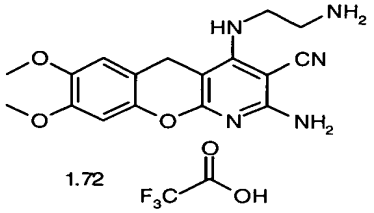
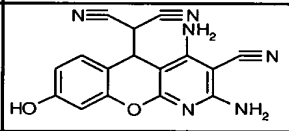
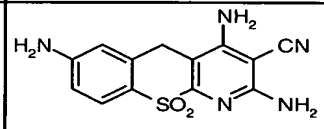
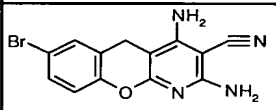
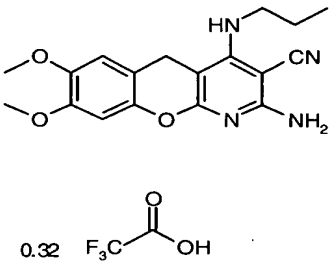
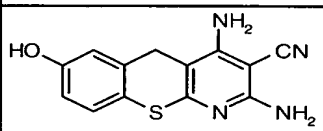
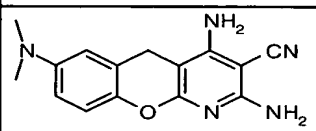
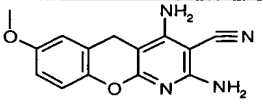
8		2,4-diamino-9-fluoro-5H-chromeno[2,3-b]pyridine-3-carbonitrile	0.471
9		2,4-diamino-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.473
10		2,4-diamino-8-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.483
11		8,10-diamino-2,3-dihydro-11H-[1,4]dioxino[2',3':6,7]chromeno[2,3-b]pyridine-9-carbonitrile trifluoroacetate	0.488
12		2,4,7-triamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile	0.514
13		2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.563
14		2,4-diamino-8-(2-ethoxyethoxy)-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.62
15		2,4-diamino-9-hydroxy-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.682

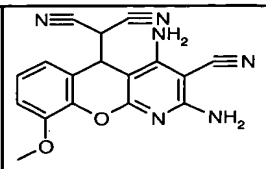
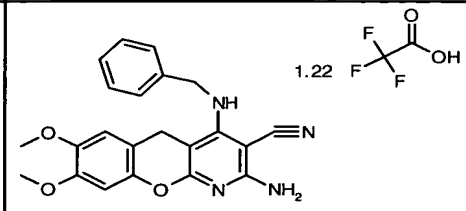
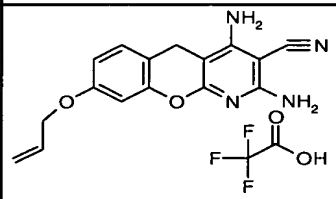
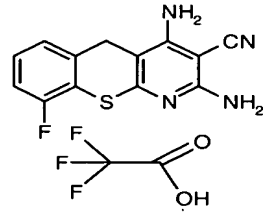
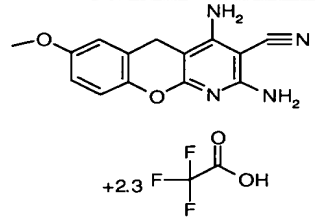
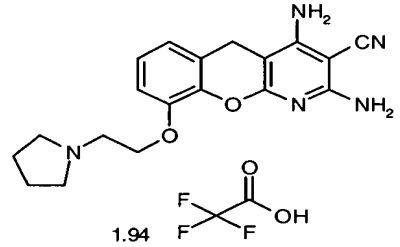
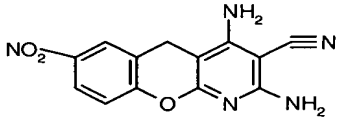
16		2,4-diamino-6,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.694
17		2,4-diamino-8-ethoxy-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.773
18		2,4-diamino-8-(2-ethoxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	0.817
19		2,4-diamino-8-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile hydrochloride	0.82
20		2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-7-carboxylic acid trifluoroacetate	0.857
21		2,4-diamino-8,9-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.857
22		2,4-diamino-8-(2-morpholin-4-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.91
23		[(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-8-yl)oxy]acetic acid trifluoroacetate	0.916

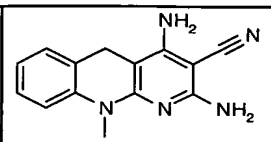
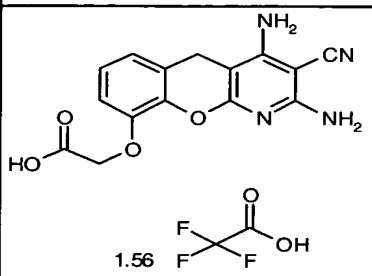
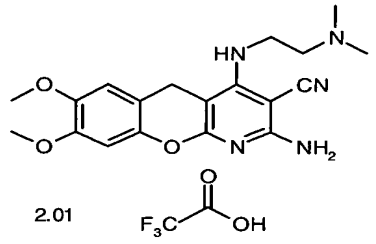
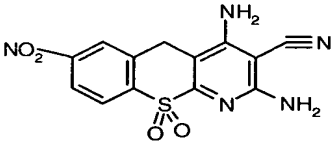
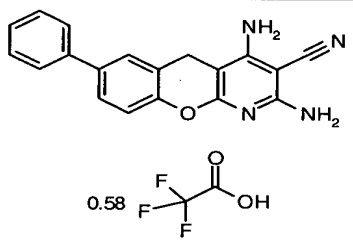
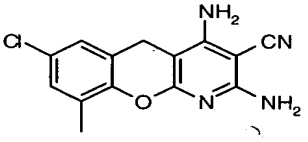
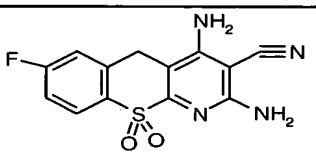
24		2,4-diamino-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	1.37
25		2,4-diamino-8-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	1.68
26		2-amino-7,8-dimethoxy-4-(methylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile bis(trifluoroacetate)	1.69
27		2,4-diamino-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	1.72
28		2,4-diamino-8-[2-(dimethylamino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	1.75
29		2,4,7-triamino-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	1.79
30		2(2,4-diamino-3-cyano-8-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	1.94
31		2,4-diamino-7,8-di[2-(amino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	2.55

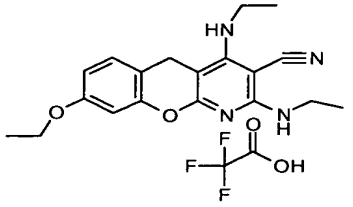
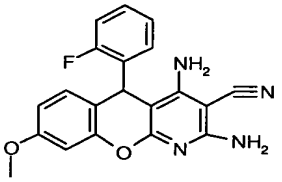
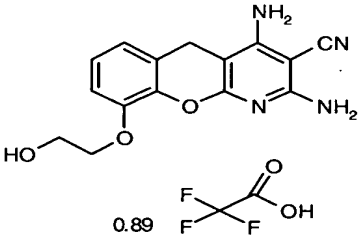
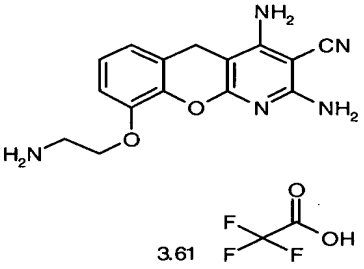
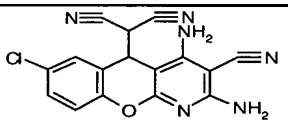
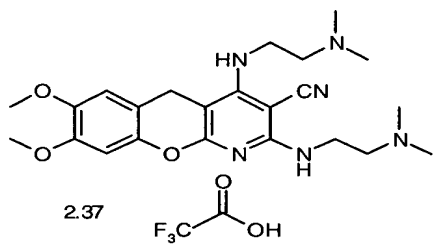
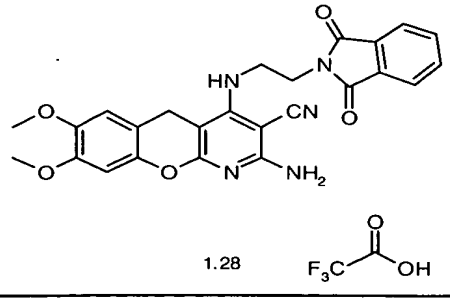
32	 0.125 CF3CO2H	2,4-diamino-9-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile	2.58
33		2-amino-7,8-dimethoxy-4-[(4-methoxyphenyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile bis(trifluoroacetate)	2.98
34	 2.3	2,4-diamino-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	3.24
35		2(2,4-diamino-3-cyano-7-hydroxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	3.8
36		2(2,4-diamino-3-cyano-7-bromo-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	4.22
37		2-amino-8-ethoxy-4-(ethylamino)-5H chromeno[2,3-b]pyridine-3-carbonitrile	4.76
38		2,4,9-triamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	5.01

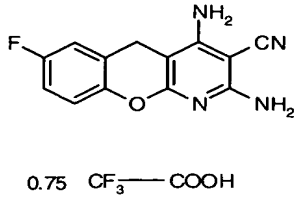
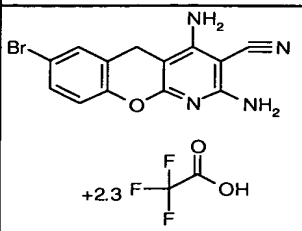
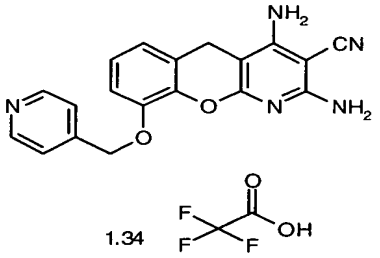
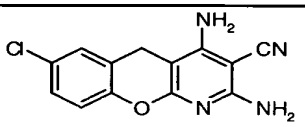
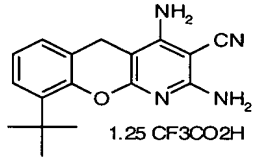
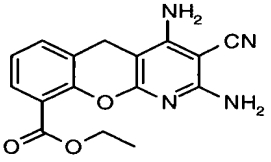
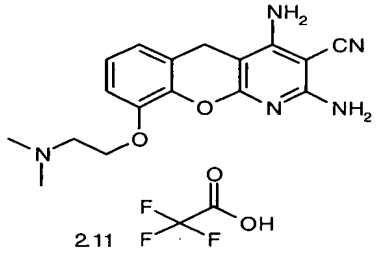
39		2,4,7-triamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	5.6
40		2-amino-7,8-dimethoxy-4-[(4-methoxyphenyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	6.11
41		2(2,4-diamino-3-cyano-7-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	6.18
42	 2.0 TFA	2,4-diamino-9-hydroxy-8-(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	8.28
43	 0.8	7,8-bis(allyloxy)-2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	9.6
44		2-amino-8-(2-ethoxyethoxy)-4-[(2-ethoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	9.66

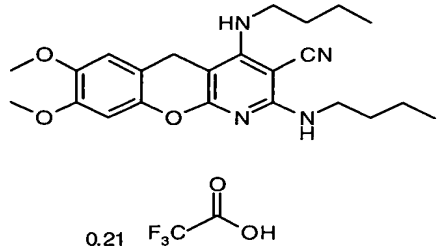
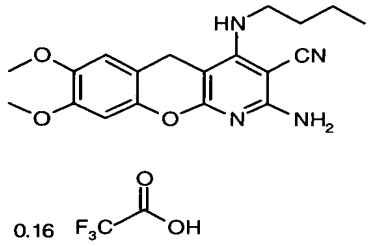
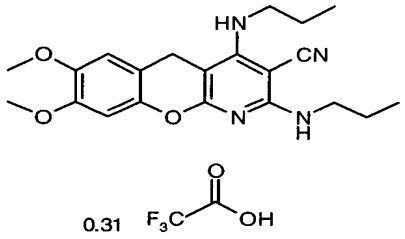
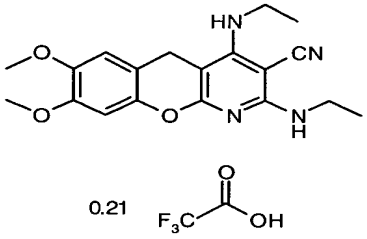
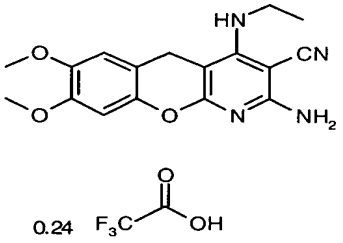
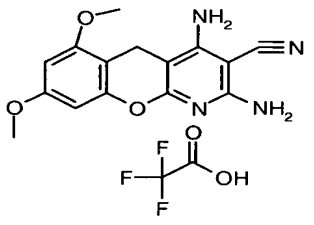
45	 1.6	tert-butyl {[2,4-diamino-7-(2-tert-butoxy-2-oxoethoxy)-3-cyano-5H-chromeno[2,3-b]pyridin-8-yl]oxy}acetate trifluoroacetate	10.3
46	 1.72	2-amino-4-[(2-aminoethyl)amino]-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	11.5
47		2(2,4-diamino-3-cyano-8-hydroxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	12.8
48		2,4,7-triamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide	14.4
49		2,4-diamino-7-bromo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	15.1
50	 0.32	2-amino-7,8-dimethoxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	15.6
51		2,4-diamino-7-hydroxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile	17.4
52		2,4-diamino-7-(dimethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	17.6
53		2,4-diamino-7-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	19.7

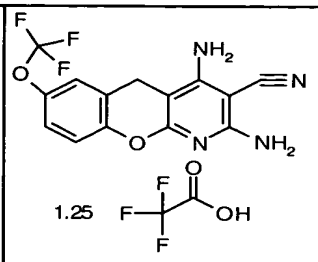
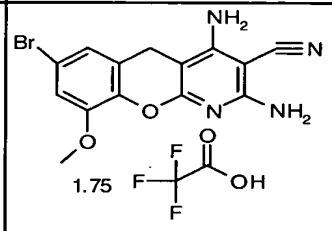
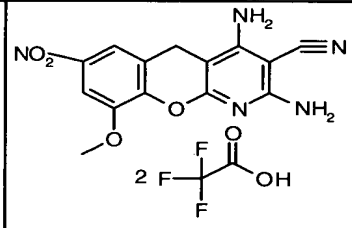
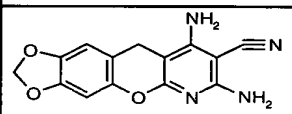
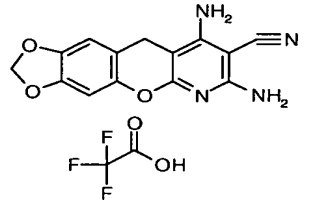
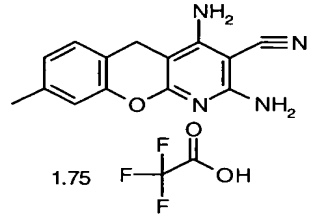
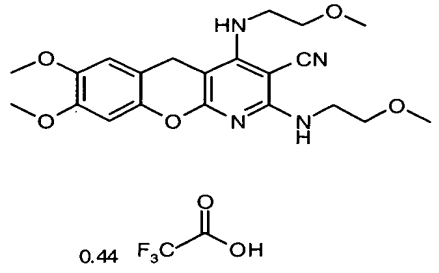
54		2(2,4-diamino-3-cyano-9-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	21.2
55		2-amino-4-(benzylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	27.4
56		8-(allyloxy)-2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	33.8
57		2,4-diamino-9-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	42.2
58		2,4-diamino-7-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	43
59		2,4-diamino-9-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	45.2
60		2,4-diamino-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile	62.2

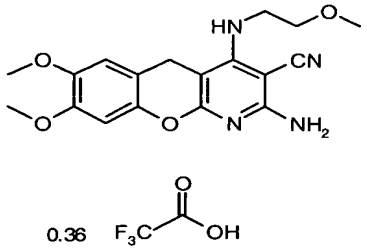
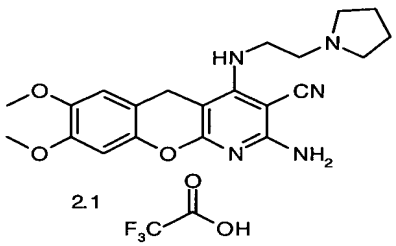
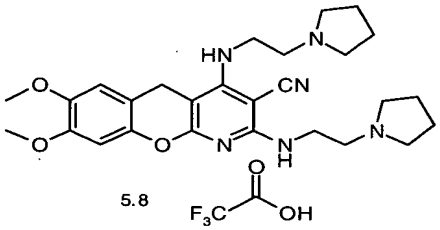
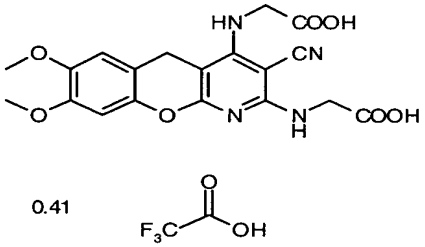
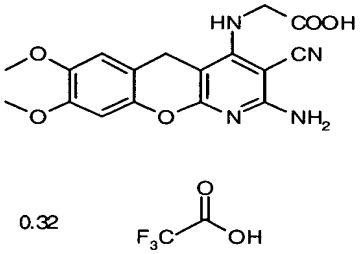
61	 2.0 TFA	2,4-diamino-10-methyl-5,10-dihydrobenzo[b]-1,8-naphthyridine-3-carbonitrile trifluoroacetate	70.1
62	 1.56	[(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-9-yl)oxy]acetic acid trifluoroacetate	72.2
63	 2.01	2-amino-4-{[2-(dimethylamino)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	79.1
64		2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide	80.8
65	 0.58	2,4-diamino-7-phenyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	83.8
66		2,4-diamino-7-chloro-9-methyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile	136
67		2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide	142

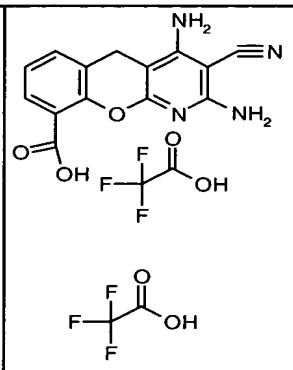
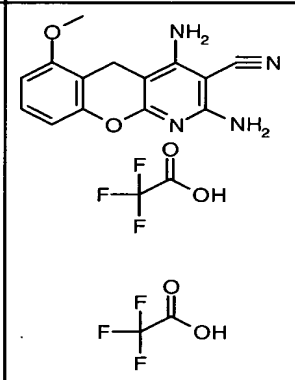
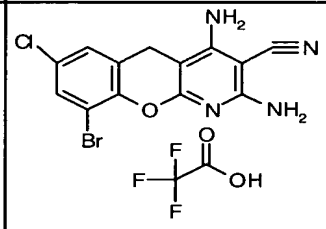
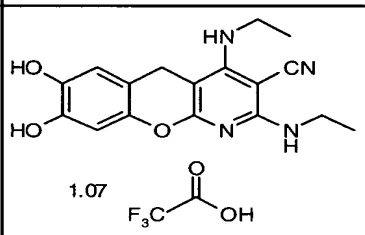
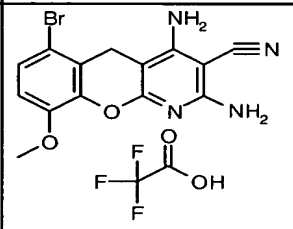
68		8-ethoxy-2,4-bis(ethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	148
69		2,4-diamino-5-(2-fluoro-phenyl)-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	151
70		2,4-diamino-9-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	154
71		2,4-diamino-9-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	161
72		2(2,4-diamino-3-cyano-7-chloro-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	200
73		2,4-bis{[2-(dimethylamino)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
74		2-amino-4-{[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200

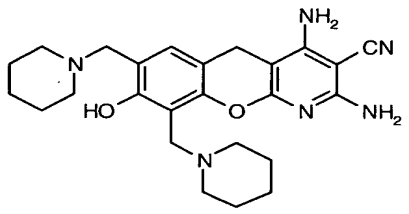
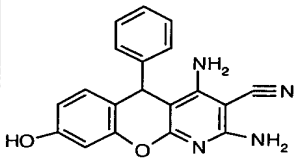
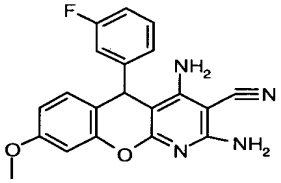
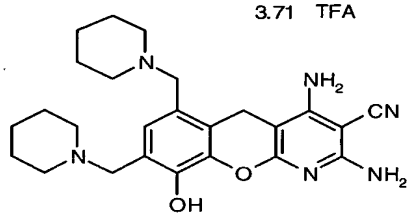
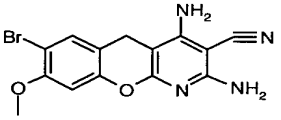
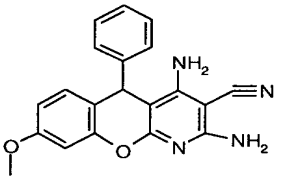
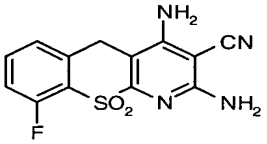
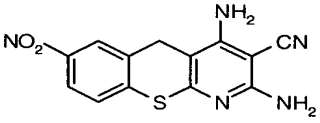
75	 0.75 CF_3—COOH	2,4-diamino-7-fluoro-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
76	 +2.3	2,4-diamino-7-bromo-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
77	 1.34	2,4-diamino-9-(pyridin-4-ylmethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
78	 1.75 CF3CO2H	2,4-diamino-7-chloro-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
79	 1.25 CF3CO2H	2,4-diamino-9-tert-butyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
80		ethyl 2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-9-carboxylate	200
81	 2.11	2,4-diamino-9-[2-(dimethylamino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200

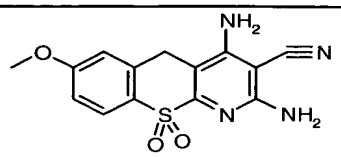
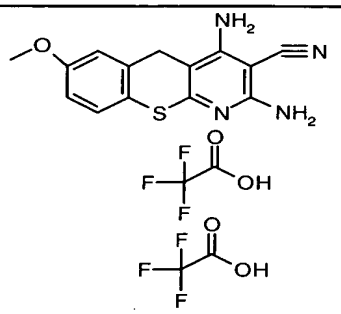
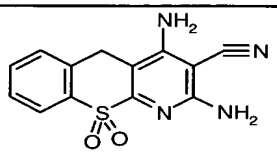
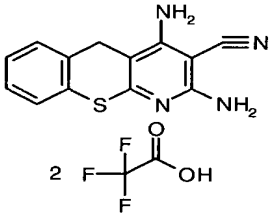
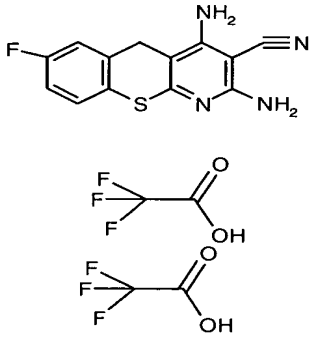
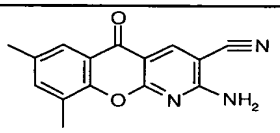
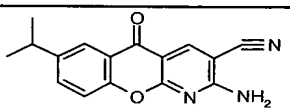
82		2,4-bis(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
83		2-amino-4-(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
84		7,8-dimethoxy-2,4-bis(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
85		2,4-bis(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
86		2-amino-4-(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
87		2,4-diamino-6,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200

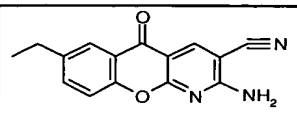
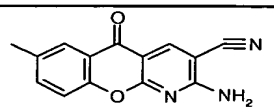
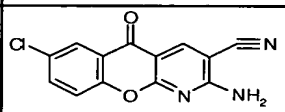
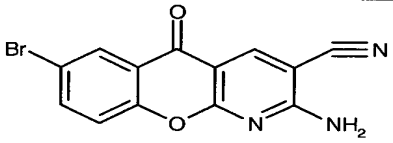
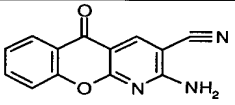
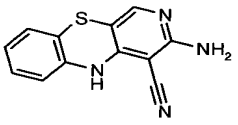
88		2,4-diamino-7-(trifluoromethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
89		2,4-diamino-7-bromo-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
90		2,4-diamino-9-methoxy-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
91		7,9-diamino-10H-[1,3]dioxolo[6,7]chromeno[2,3-b]pyridine-8-carbonitrile	200
92		7,9-diamino-10H-[1,3]dioxolo[6,7]chromeno[2,3-b]pyridine-8-carbonitrile trifluoroacetate	200
93		2,4-diamino-8-methyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
94		7,8-dimethoxy-2,4-bis[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200

95	 0.36	2-amino-7,8-dimethoxy-4-[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
96	 2.1	2-amino-7,8-dimethoxy-4-[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
97	 5.8	7,8-dimethoxy-2,4-bis[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
98	 0.41	2,4-bis(glycinyl)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
99	 0.32	N-(2-amino-3-cyano-7,8-dimethoxy-5H-chromeno[2,3-b]pyridin-4-yl)glycine	200

100		2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-9-carboxylic acid bis(trifluoroacetate)	200
101		2,4-diamino-6-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile bis(trifluoroacetate)	200
102		2,4-diamino-9-bromo-7-chloro-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
103		2,4-bis(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
104		2,4-diamino-6-bromo-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200

105	3.76 TFA 	2,4-diamino-8-hydroxy-7,9-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
106		2,4-diamino-5-phenyl-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
107		2,4-diamino-5-(3-fluoro-phenyl)-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
108	3.71 TFA 	2,4-diamino-9-hydroxy-6,8-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
109		2,4-diamino-7-bromo-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
110		2,4-diamino-5-phenyl-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
111		2,4-diamino-9-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide	200
112		2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile	200

113		2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide	200
114		2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile bis(trifluoroacetate)	200
115		2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide	200
116		2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
117		2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile bis(trifluoroacetate)	200
118		2-amino-7,9-dimethyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
119		2-amino-7-isopropyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200

120		2-amino-7-ethyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
121		2-amino-7-methyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
122		2-amino-7-chloro-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
123		2-amino-7-bromo-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
124		2-amino-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
125		3-amino-5H-pyrido[3,4-b][1,4]benzothiazine-4-carbonitrile	200

Notes:

a: The aminocyanopyridine compound may be shown with a solvent, such as, for example, trifluoroacetate, with which it can form a salt. Both the salt and acid forms of the aminocyanopyridine compound are included in the present invention.

b: Compound names generated by ACD/Name software.

[00039] In another embodiment, the present aminocyanopyridine compound has the structure shown in formula I, where:

R^1 is selected from the group consisting of hydrogen, branched or unbranched alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, arylalkyl, carboxy, carboxyalkyl, hydroxyalkyl, alkylcarboxy, aryl, amino, aminoalkyl, alkylamino, halo, alkylaminoalkyl, alkoxy, alkoxyalkyl, monocyclyl, bicyclyl, polycyclyl, and heterocyclyl;

R^2 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkylaryl, arylalkyl, alkoxyaryl, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, alkoxyalkyl, alkylcarboxy, and carboxyalkyl;

R^3 is selected from the group consisting of hydrogen, dicyanoalkyl, and substituted or unsubstituted heterocyclyl and cyclyl, where substituents, if any, comprise halo moieties;

R^4 is selected from the group consisting of hydrogen, dicyanoalkyl, and substituted or unsubstituted heterocyclyl and cyclyl, where substituents, if any, comprise halo moieties;

R^5 is selected from the group consisting of hydrogen, alkoxy, halo, alkyl, alkenyl, alkylyl, arylalkyl, or alkylaryl;

R^6 is selected from the group consisting of hydrogen, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, amino, alkylamino, arylamino, alkylaminoalkyl, carboxy, aminoalkoxy, halo, alkylcarboxyalkyl, alkylamino, aminoalkyl, nitro, aryl, arylalkyl, alkylaryl, or arylamino;

R^7 is selected from the group consisting of hydrogen, hydroxy, alkoxy, alkenoxy, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, heterocyclylalkyl, heterocyclylalkoxy, carboxyalkoxy, alkylaminoalkoxy, and alkylcarboxyalkoxy;

where the R^6 and R^7 groups optionally join to form a six membered heterocyclic ring;

R^8 is selected from the group consisting of hydrogen, hydroxy, halo, nitro, amino, alkyl, alkoxy, heterocyclylalkoxy, carboxyalkoxy,

pyrrolidylethoxy, carboxymethoxy, hydroxyalkoxy, aminoalkoxy, alkylcarboxy, alkylaminoalkyl, carboxy, and heterocyclylalkyl; and

G is selected from the group consisting of oxygen, sulfur, and nitrogen;

when G is oxygen, R^9 and R^{10} are absent;

when G is sulfur, each of R^9 and R^{10} is optionally absent, or is oxo;

when G is nitrogen, R^9 is absent, and R^{10} is C_1-C_4-alkyl.

[00040] In another embodiment, the present aminocyanopyridine compound can have the structure shown in formula I, where:

R^1 is selected from the group consisting of hydrogen, ethyl, dimethylaminoethyl, butyl, propyl, methoxyethyl, tetramethylaminoethyl, and carboxymethyl;

R^2 is selected from the group consisting of hydrogen, hydroxyethyl, propyl, ethyl, methyl, 4-methoxyphenyl, ethoxyethyl, aminoethyl, phenylmethyl, dimethylaminoethyl, phthaloaminoethyl, butyl, methoxyethyl, tetramethylaminoethyl, and carboxymethyl;

R^3 is selected from the group consisting of hydrogen, dicyanomethyl, 2-fluorophenyl, phenyl, and 3-fluorophenyl.

R^4 is selected from the group consisting of hydrogen, dicyanomethyl, 2-fluorophenyl, phenyl, and 3-fluorophenyl;

R^5 is selected from the group consisting of hydrogen, hydroxy, methoxy, bromo, and 2-pyridomethyl;

R^6 is selected from the group consisting of hydrogen, hydroxy, methoxy, amino, carboxy, diaminoethoxy, bromo, propoxy, isobutylcarboxymethoxy, dimethylamino, nitro, phenyl, chloro, pyridylmethyl, and fluoro;

R^7 is selected from the group consisting of hydrogen, hydroxy, methoxy, hydroxyethoxy, ethoxyethoxy, ethoxy, aminoethoxy, morpholinoethoxy, carboxymethoxy, *N*-pyrrolidylethoxy, dimethylaminoethoxy, pyridylmethyl, 2-propenoxy, and isobutylcarboxymethoxy, where the R^6 and R^7 groups optionally join to form a six membered heterocyclic ring;

R^8 is selected from the group consisting of hydrogen, hydroxy, fluoro, methoxy, nitro, amino, pyrrolidylethoxy, carboxymethoxy, methyl, hydroxyethoxy, aminoethoxy, 4-pyridylmethoxy, isobutyl, ethylcarboxy, dimethylaminoethoxy, carboxy, bromo, and pyrridylmethyl; and

G is selected from the group consisting of oxygen, sulfur, and nitrogen;

when G is oxygen, R^9 and R^{10} are absent;

when G is sulfur, each of R^9 and R^{10} is optionally absent, or is oxo;

when G is nitrogen, R^9 is absent, and R^{10} is $-CH_3$.

[00041] In another embodiment, the present aminocyanopyridine compound can provide an IC_{50} of less than about 200 μM, in an *in vitro* assay of MK-2 inhibitory activity. Examples of such compounds comprise the compound shown in formula I, where:

R^1 is selected from the group consisting of hydrogen, and C_1-C_2 alky;

R^2 is selected from the group consisting of hydrogen, C_1-C_3 alkyl, hydroxy C_1-C_2 alkyl, C_1-C_2 alkoxyphenyl, C_1-C_2 alkoxy C_1-C_2 alkyl, amino C_1-C_2 alkyl, phenyl C_1-C_2 alkyl, and di C_1-C_2 alkylamino C_1-C_2 alkyl;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, dicyano C_1-C_2 alkyl, and halophenyl;

R^5 is selected from the group consisting of hydrogen, and hydroxy;

R^6 is selected from the group consisting of hydrogen, hydroxy, C_1 - C_3 alkoxy, amino, nitro, carboxy, diamino C_1 - C_2 alkoxy, halo, propenoxy, iso C_3 - C_4 alkylcarboxy C_1 - C_2 alkoxy, di C_1 - C_2 alkylamino, and phenyl;

R^7 is selected from the group consisting of hydrogen, hydroxy, C_1 - C_3 alkoxy, hydroxy C_1 - C_2 alkoxy, C_1 - C_2 alkoxy C_1 - C_2 alkoxy, amino C_1 - C_2 alkoxy, morpholino C_1 - C_2 alkoxy, carboxyl C_1 - C_2 alkoxy, pyrrolidyl C_1 - C_2 alkoxy, di C_1 - C_2 alkylamino C_1 - C_2 alkoxy, pyrrolidyl C_1 - C_2 alkyl, iso C_3 - C_4 alkylcarboxy C_1 - C_2 alkoxy, and $_2$-propenoxy,

where the R^6 and R^7 groups optionally join to form a six membered heterocyclic ring;

R^8 is selected from the group consisting of hydrogen, hydroxy, halo, C_1-C_2 alkyl, C_1-C_2 alkoxy, nitro, amino, pyrrolidyl C_1-C_2 alkoxy, carboxy C_1-C_2 alkoxy, hydroxy C_1-C_2 alkoxy, and amino C_1-C_2 alkoxy; and

G is selected from the group consisting of oxygen and sulfur;

when G is sulfur, each of R^9 and R^{10} is optionally absent, or is oxo;

when G is oxygen, R^9 and R^{10} are absent.

[00042] In another embodiment, the present aminocyanopyridine compound can provide an IC_{50} of less than about 100 μM, in an *in vitro* assay of MK-2 inhibitory activity. Examples of such compounds comprise the compound shown in formula I, where:

R^1 is hydrogen;

R^2 is selected from the group consisting of hydrogen, C_1 - C_3 alkyl, hydroxy C_1 - C_2 alkyl, C_1 - C_2 alkoxyphenyl, C_1 - C_2 alkoxy C_1 - C_2 alkyl, amino C_1 - C_2 alkyl, phenyl C_1 - C_2 alkyl, and di C_1 - C_2 alkylamino C_1 - C_2 alkyl;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, and dicyano C_1 - C_2 alkyl.

R^5 is selected from the group consisting of hydrogen, and hydroxy;

R^6 is selected from the group consisting of hydrogen, hydroxy, C_1-C_2 alkoxy, amino, carboxy, nitro, diamino C_1-C_2 alkoxy, halo, 2-propenoxy, iso C_3-C_4 alkylcarboxy C_1-C_2 alkoxy, di C_1-C_2 alkylamino, and phenyl;

R^7 is selected from the group consisting of hydrogen, hydroxy, C_1 - C_2 alkoxy, hydroxy C_1-C_2 alkoxy, C_1-C_2 alkoxy C_1-C_2 alkoxy, amino C_1-C_2 alkoxy, morpholino C_1-C_2 alkoxy, carboxyl C_1-C_2 alkoxy, pyrrolidyl C_1-C_2 alkoxy, di C_1-C_2 alkylamino C_1-C_2 alkoxy, pyrrolidyl C_1-C_2 alkyl, iso C_3-C_4 alkylcarboxy C_1-C_2 alkoxy, and 2-propenoxy;

wherein the R^6 and R^7 groups optionally join to form a six membered heterocyclic ring;

R^8 is selected from the group consisting of hydrogen, hydroxy, halo, C_1-C_2 alkoxy, nitro, amino, pyrrolidyl C_1-C_2 alkoxy, and carboxy C_1-C_2 alkoxy; and

G is selected from the group consisting of oxygen and sulfur;

when G is sulfur, each of R^9 and R^{10} is optionally absent, or is oxo;

when G is oxygen, R^9 and R^{10} are absent.

[00043] In another embodiment, the present aminocyanopyridine compound can provide an IC_{50} of less than about 50 μM, in an *in vitro* assay of MK-2 inhibitory activity. Examples of such compounds comprise the compound shown in formula I, where:

R^1 is hydrogen;

R^2 is selected from the group consisting of hydrogen, C_1-C_3 alkyl, hydroxy C_1-C_2 alkyl, C_1-C_2 alkoxyphenyl, C_1-C_2 alkoxy C_1-C_2 alkyl, amino C_1-C_2 alkyl, and phenyl C_1-C_2 alkyl;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, and dicyano C_1-C_2 alkyl.

R^5 is selected from the group consisting of hydrogen, and hydroxy;

R^6 is selected from the group consisting of hydrogen, hydroxy, C_1-C_2 alkoxy, amino, carboxy, diamino C_1-C_2 alkoxy, halo, 2-propenoxy, iso C_3-C_4 alkylcarboxy C_1-C_2 alkoxy, and di C_1-C_2 alkylamino;

R^7 is selected from the group consisting of hydrogen, hydroxy, C_1-C_2 alkoxy, hydroxy C_1-C_2 alkoxy, C_1-C_2 alkoxy C_1-C_2 alkoxy, amino C_1-C_2 alkoxy, morpholino C_1-C_2 alkoxy, carboxyl C_1-C_2 alkoxy, pyrrolidyl C_1-C_2 alkoxy, di C_1-C_2 alkylamino C_1-C_2 alkoxy, pyrrolidyl C_1-C_2 alkyl, iso C_3-C_4 alkylcarboxy C_1-C_2 alkoxy, and 2-propenoxy;

where the R^6 and R^7 groups optionally join to form a six membered heterocyclic ring;

R^8 is selected from the group consisting of hydrogen, hydroxy, halo, C_1-C_2 alkoxy, nitro, amino, and pyrrolidyl C_1-C_2 alkoxy; and

G is selected from the group consisting of oxygen and sulfur;

when G is sulfur, each of R^9 and R^{10} is optionally absent, or is oxo;

when G is oxygen, there R^9 and R^{10} are absent.

[00044] In another embodiment, the present aminocyanopyridine compound can provide an IC_{50} of less than about 20 μM, in an *in vitro* assay of MK-2 inhibitory activity. Examples of such compounds comprise the compound shown in formula I, where:

R^1 is hydrogen;

R^2 is selected from the group consisting of hydrogen, C_1-C_3 alkyl, hydroxy C_1-C_2 alkyl, C_1-C_2 alkoxyphenyl, C_1-C_2 alkoxy C_1-C_2 alkyl, and amino C_1-C_2 alkyl;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, and dicyanoethyl;

R^5 is selected from the group consisting of hydrogen, and hydroxy;

R^6 is selected from the group consisting of hydrogen, hydroxy, C_1-C_2 alkoxy, amino, carboxy, diamino C_1-C_2 alkoxy, halo, 2-propenoxy, iso C_3-C_4 alkylcarboxy C_1-C_2 alkoxy, and di C_1-C_2 alkylamino;

R^7 is selected from the group consisting of hydrogen, hydroxy, C_1-C_2 alkoxy, hydroxy C_1-C_2 alkoxy, C_1-C_2 alkoxy C_1-C_2 alkoxy, amino C_1-C_2 alkoxy, morpholino C_1-C_2 alkoxy, carboxyl C_1-C_2 alkoxy, pyrrolidyl C_1-C_2 alkoxy, di C_1-C_2 alkylamino C_1-C_2 alkoxy, pyrrolidyl C_1-C_2 alkyl, iso C_3-C_4 alkylcarboxy C_1-C_2 alkoxy, and 2-propenoxy;

where the R^6 and R^7 groups optionally join to form a six membered heterocyclic ring;

R^8 is selected from the group consisting of hydrogen, hydroxy, halo, methoxy, nitro, and amino; and

G is selected from the group consisting of oxygen and sulfur;

when G is sulfur, each of R^9 and R^{10} is optionally absent, or is oxo;

when G is oxygen, R^9 and R^{10} are absent.

[00045] Examples of aminocyanopyridine MK-2 inhibitor compounds of the present invention include, without limitation, the following:

2,4-diamino-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

2-amino-7,8-dihydroxy-4-[(2-hydroxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

2,4-diamino-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

2-amino-7,8-dihydroxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

2-amino-4-(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-fluoro-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-8-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
8,10-diamino-2,3-dihydro-11H-[1,4]dioxino[2',3':6,7]chromeno[2,3-b]pyridine-9-carbonitrile,
2,4,7-triamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile
2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-8-(2-ethoxyethoxy)-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-hydroxy-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-6,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-8-ethoxy-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-8-(2-ethoxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-8-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-7-carboxylic acid,
2,4-diamino-8,9-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-8-(2-morpholin-4-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
[(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-8-yl)oxy]acetic acid,
2,4-diamino-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-8-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7,8-dimethoxy-4-(methylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

2,4-diamino-8-[2-(dimethylamino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4,7-triamino-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2(2,4-diamino-3-cyano-8-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile,
2,4-diamino-7,8-di[2-(amino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7,8-dimethoxy-4-[(4-methoxyphenyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2(2,4-diamino-3-cyano-7-hydroxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile,
2(2,4-diamino-3-cyano-7-bromo-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile,
2-amino-8-ethoxy-4-(ethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4,9-triamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4,7-triamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7,8-dimethoxy-4-[(4-methoxyphenyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2(2,4-diamino-3-cyano-7-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile,
2,4-diamino-9-hydroxy-8-(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
7,8-bis(allyloxy)-2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-8-(2-ethoxyethoxy)-4-[(2-ethoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
tert-butyl {[2,4-diamino-7-(2-tert-butoxy-2-oxoethoxy)-3-cyano-5H-chromeno[2,3-b]pyridin-8-yl]oxy}acetate,
2-amino-4-[(2-aminoethyl)amino]-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

2(2,4-diamino-3-cyano-8-hydroxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile,
2,4,7-triamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide,
2,4-diamino-7-bromo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7,8-dimethoxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-hydroxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-(dimethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2(2,4-diamino-3-cyano-9-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile,
2-amino-4-(benzylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
8-(allyloxy)-2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-10-methyl-5,10-dihydrobenzo[b]-1,8-naphthyridine-3-carbonitrile,
[(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-9-yl)oxy]acetic acid,
2-amino-4-{[2-(dimethylamino)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide,
2,4-diamino-7-phenyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-chloro-9-methyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide,
8-ethoxy-2,4-bis(ethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

2,4-diamino-5-(2-fluoro-phenyl)-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2(2,4-diamino-3-cyano-7-chloro-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile,
2,4-bis{[2-(dimethylamino)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-4-{[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-fluoro-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-bromo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-(pyridin-4-ylmethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-chloro-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-tert-butyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
ethyl 2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-9-carboxylate,
2,4-diamino-9-[2-(dimethylamino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-bis(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-4-(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
7,8-dimethoxy-2,4-bis(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-bis(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-4-(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-6,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

2,4-diamino-7-(trifluoromethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-bromo-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-methoxy-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
7,9-diamino-10H-[1,3]dioxolo[6,7]chromeno[2,3-b]pyridine-8-carbonitrile,
7,9-diamino-10H-[1,3]dioxolo[6,7]chromeno[2,3-b]pyridine-8-carbonitrile,
2,4-diamino-8-methyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
7,8-dimethoxy-2,4-bis[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7,8-dimethoxy-4-[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7,8-dimethoxy-4-[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
7,8-dimethoxy-2,4-bis[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-bis(glycinyl)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
N-(2-amino-3-cyano-7,8-dimethoxy-5H-chromeno[2,3-b]pyridin-4-yl)glycine,
2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-9-carboxylic acid,
2,4-diamino-6-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-bromo-7-chloro-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-bis(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-6-bromo-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-8-hydroxy-7,9-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-5-phenyl-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-5-(3-fluoro-phenyl)-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

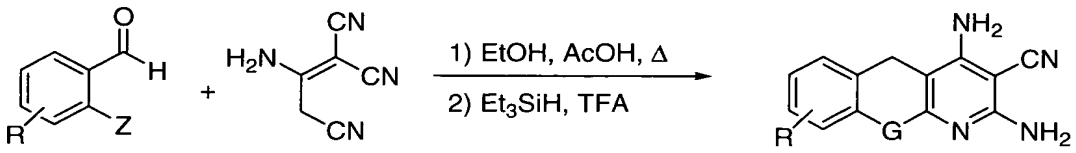
2,4-diamino-9-hydroxy-6,8-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-bromo-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-5-phenyl-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide,
2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide, 2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide,
2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7,9-dimethyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7-isopropyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7-ethyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7-methyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7-chloro-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7-bromo-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile, and
3-amino-5H-pyrido[3,4-b][1,4]benzothiazine-4-carbonitrile.

[00046] It should be understood that salts and prodrugs of the aminocyanopyridine compounds that are described herein, as well as isomeric forms, tautomers, racemic mixtures of the compounds, and the like, which have the same or similar activity as the compounds that are described, are to be considered to be included within the description of the compound.

[00047] Aminocyanopyridine MK-2 inhibiting compounds of the type shown in formula I, above, include tricyclic aminocyanopyridine MK-2 inhibiting compounds, such as benzonapthyridines, pyridochromanes, and

pyridothiochromanes. A general method for the synthesis of these tricyclic aminocyanopyridines is shown in Scheme 1, below:

Scheme 1:



Z = OH, SH, NR^aY

G = O, S, NR^a

[00048] In this method, a substituted benzaldehyde is reacted with a tricarbonitrile, preferably 2-amino-1-propene-1,1,3-tricarbonitrile. The reaction can be carried out by heating the reactants to reflux in a solution of acetic acid and ethanol. The reaction product can be concentrated *in vacuo* and dissolved in trifluoroacetic acid. Triethylsilane is added and the mixture is stirred. In a preferred method, the mixture is stirred for about 1 hour at 0°C. Dichloromethane is then added and solids are collected. The solids can be collected by filtration, and can be washed with dichloromethane and ether. The solids comprise the desired tricyclic aminocyanopiyridine MK-2 inhibiting compound of the type including benzonapthyridines, pyridochromanes, and pyridothiochromanes.

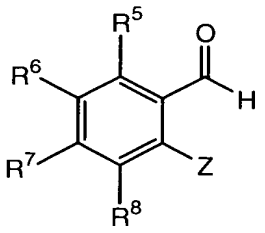
[00049] Referring to the reactants and products shown above in Scheme I:

Z can be OH, SH, or NR^aY, where Y is a protecting group for nitrogen. The Y group can be benzyl, allyl, an alkyl carbamate, or a benzyl carbamate. Other nitrogen protecting groups are know to persons having skill in the art of organic synthesis. A perferred protecting group is tert-butylcarbamate. R^a can be an alkyl group, an aryl group, or a heteroaryl group. The benzene ring of the benzaldehyde can be further substituted by one, two, three, or four additional R groups at carbons 3, 4, 5, or 6. Each R can independently be hydrogen; alkyl; aryl; a heteroatom, such as O, N, or S, substituted with hydrogen, C_1-C_6 alkyl, C_1-C_6 branched alkyl, aryl, heteroaryl (wherein the heteroaryl can include, but is not limited to,

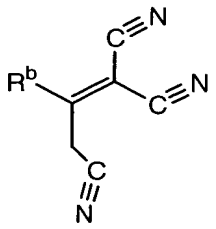
pyrazolyl, inidizolyl, pyrryl, pyridyl, thiophyl, furyl and pyrimidyl), ester and amido.

[00050] Advantages of this method include that it is a general method that can be used to produce various types of the tricyclic compounds of formula I depending upon the types of reactants used. It is also an easy and straightforward synthesis method that can be carried out in a single vessel.

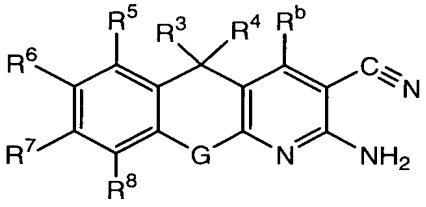
[00051] In an embodiment of this method of synthesis, a tricyclic aminocyanopyridine MK-2 inhibiting compound can be prepared by reacting a substituted benzaldehyde having the structure:



with a tricarbonitrile having the structure:



to form an aminocyanopyridine compound having the structure:



wherein:

Z is selected from the group consisting of -OH, -SH, and -NR^aY;

R_a is selected from the group consisting of alkyl, aryl, and heteroaryl;

Y is a protecting group for nitrogen. Examples of such nitrogen protecting groups include benzyl, allyl, alkyl carbamates and benzyl carbamates.

G is selected from the group consisting of oxygen, sulfur, and nitrogen;

when G is oxygen, it has no substituent groups;

when G is sulfur, it is either unsubstituted, or is substitutued with one or two oxo groups;

when G is nitrogen, it is substituted with C_1-C_4 alkyl;

R^b is selected from the group consisting of furyl and -NH-R^2;

R^2 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkylaryl, arylalkyl, alkoxyaryl, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, alkoxyalkyl, alkylcarboxy, and carboxyalkyl;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, dicyanoalkyl, and substituted or unsubstituted heterocyclyl and cyclyl, where substituents, if any, comprise halo moieties; and

R^5, R^6, R^7 and R^8 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, halo, alkyl, alkenyl, alkylyl, arylalkyl, alkylaryl, amino, alkylamino, arylamino, alkylaminoalkyl, carboxy, aminoalkoxy, alkylcarboxyalkyl, alkylamino, aminoalkyl, nitro, aryl, arylamino, alkenoxy, hydroxyalkoxy, alkoxyalkoxy, heterocyclylalkyl, heterocyclylalkoxy, carboxyalkoxy, alkylaminoalkoxy, alkylcarboxyalkoxy, pyrrolidylethoxy, hydroxyalkoxy, and alkylcarboxy, where R^6 and R^7 are such that they optionally join to form a six membered heterocyclic ring.

[00052] In an embodiment of the general method described above,

R^2 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkylaryl, arylalkyl, alkoxyaryl, aminoalkyl,

alkylaminoalkyl, arylaminoalkyl, alkoxyalkyl, alkylcarboxy, and carboxyalkyl;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, dicyanoalkyl, and substituted or unsubstituted heterocyclyl and cyclyl, where substituents, if any, comprise halo moieties;

R^5 is selected from the group consisting of hydrogen, alkoxy, halo, alkyl, alkenyl, alkylyl, arylalkyl, or alkylaryl;

R^6 is selected from the group consisting of hydrogen, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, amino, alkylamino, arylamino, alkylaminoalkyl, carboxy, aminoalkoxy, halo, alkylcarboxyalkyl, alkylamino, aminoalkyl, nitro, aryl, arylalkyl, alkylaryl, or arylamino;

R^7 is selected from the group consisting of hydrogen, hydroxy, alkoxy, alkenoxy, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, heterocyclylalkyl, heterocyclylalkoxy, carboxyalkoxy, alkylaminoalkoxy, and alkylcarboxyalkoxy;

where the R^6 and R^7 groups optionally join to form a six membered heterocyclic ring; and

R^8 is selected from the group consisting of hydrogen, hydroxy, halo, nitro, amino, alkyl, alkoxy, heterocyclylalkoxy, carboxyalkoxy, pyrrolidylethoxy, carboxymethoxy, hydroxyalkoxy, aminoalkoxy, alkylcarboxy, alkylaminoalkyl, carboxy, and heterocyclylalkyl.

[00053] In a preferred embodiment of this method, the substituted benzaldehyde comprises salicaldehyde and the tricarbonitrile comprises 2-amino-1-propene-1,1,3-tricarbonitrile. It is also preferred that the nitrogen protecting group "Y", comprises tert-butylcarbamate.

[00054] In an embodiment of the present method,

Z is selected from the group consisting of -OH, -SH, and $-NR^aY$;

R_a is selected from the group consisting of alkyl, aryl, and heteroaryl;

Y is a protecting group for nitrogen that is selected from the group consisting of benzyl, allyl, alkyl carbamates and benzyl carbamate;

G is selected from the group consisting of oxygen, sulfur, and nitrogen;

when G is oxygen, it has no substituent groups;

when G is sulfur, it is either unsubstituted, or is substitutued with one or two oxo groups;

when G is nitrogen, it is substituted with C_1-C_4 alkyl;

R^b is selected from the group consisting of furyl and -NH-R^2;

R^2 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkylaryl, arylalkyl, alkoxyaryl, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, alkoxyalkyl, alkylcarboxy, and carboxyalkyl;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, dicyanoalkyl, and substituted or unsubstituted heterocyclyl and cyclyl, where substituents, if any, comprise halo moieties; and

R^5, R^6, R^7 and R^8 are each independently selected from the group consisting of:

hydrogen, hydroxy, amino, halo, nitro,

branched or unbranched C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, hydroxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_2-C_6 alkenoxy,

branched or unbranched amino C_1-C_6 alkyl, diamino C_2-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, C_1-C_6 alkylamino, di-(C_1-C_6 alkyl)amino, C_1-C_4 alkoxyarylamino, C_1-C_4 alkoxyalkylamino, amino C_1-C_6 alkoxy, di-(C_1-C_4 alkylamino, C_2-C_6 alkoxy, di-(C_1-C_6 alkyl)amino C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkoxy, halo C_1-C_6 alkoxy, dihalo C_1-C_6 alkoxy, trihalo C_1-C_6 alkoxy, cyano C_1-C_6 alkyl, dicyano C_1-C_6 alkyl, cyano C_1-C_6 alkoxy, dicyano C_1-C_6 alkoxy, carbamyl C_1-C_4 alkoxy, heterocyclyl C_1-C_4 alkoxy, heteroaryl C_1-C_4 alkoxy, sulfo, sulfamyl, C_1-C_4 alkylaminosulfonyl, hydroxy C_1-C_4 alkylaminosulfonyl, di-(C_1-C_4 alkyl)aminosulfonyl, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylsulfinyl,

aryl, aryl C_1-C_6 alkyl, heterocyclyl C_1-C_6 alkyl, heteroaryl C_1-C_6 alkyl, heterocyclyl C_1-C_6 alkoxy, heteroaryl C_1-C_6 alkoxy, aryl C_1-C_6 alkoxy, where the aryl ring can be substituted or unsubstituted, and, if substituted, the substituent group is selected from one or more of the group consisting of C_1-C_6 alkyl, halo, amino, and C_1-C_6 alkoxy,

substituted or unsubstituted C_3-C_6 cyclyl, C_3-C_6 heterocyclyl, and, if substituted, the substituent group is selected from one or more of the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, amino, and where the C_3-C_6 heterocyclyl ring contains O, S, or N,

branched or unbranched C_1-C_6 alkoxycarbonyl C_1-C_6 alkoxy, and

carboxy, carboxy C_1-C_6 alkoxy, carboxy C_1-C_6 alkyl, hydroxy C_1-C_4 alkoxycarbonyl, C_1-C_4 alkoxycarbonyl.

[00055] And where the terms "alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, haloalkoxy, halo, alkylthio, alkylthioalkyl, heterocyclyl, cyclyl, aryl, heteroaryl, cycloaryl, and oxo" have the same meanings as described above.

[00056] Further details of the synthesis of aminocyanopyridines are provided in the examples.

[00057] The MK-2 inhibiting activity of an aminocyanopyridine compound can be determined by any one of several methods that are well known to those having skill in the art of enzyme activity testing. One such method is described in detail in the general methods section of the examples. In addition, the efficacy of an aminocyanopyridine MK-2 inhibiting compound in therapeutic applications can be determined by testing for inhibition of TNFα production in cell culture and in animal model assays. In general, it is preferred that the aminocyanopyridine MK-2 inhibiting compounds of the present invention be capable of inhibiting the production and/or the release of TNFα in cell cultures and in animal models.

[00058] In another embodiment of the present invention, a pharmaceutical composition can be provided. The pharmaceutical composition contains one or more of the tricyclic aminocyanopyridine MK-

2 inhibitors that are described herein and a pharmaceutically acceptable carrier.

[00059] In another embodiment, a kit can be produced that comprises a dosage form comprising a tricyclic aminocyanopyridine MK-2 inhibitor in an amount which comprises a therapeutically effective amount. If desirable, the kit can also contain one or more other materials that are well known for use in medicaments.

[00060] As used herein, an "effective amount" means the dose or effective amount to be administered to a patient and the frequency of administration to the subject which is readily determined by one of ordinary skill in the art, by the use of known techniques and by observing results obtained under analogous circumstances. The dose or effective amount to be administered to a patient and the frequency of administration to the subject can be readily determined by one of ordinary skill in the art by the use of known techniques and by observing results obtained under analogous circumstances. In determining the effective amount or dose, a number of factors are considered by the attending diagnostician, including but not limited to, the potency and duration of action of the compounds used, the nature and severity of the illness to be treated, as well as the sex, age, weight, general health and individual responsiveness of the patient to be treated, and other relevant circumstances.

[00061] The phrase "therapeutically-effective" indicates the capability of an agent to prevent, or improve the severity of, the disorder, while avoiding adverse side effects typically associated with alternative therapies. The phrase "therapeutically-effective" is to be understood to be equivalent to the phrase "effective for the treatment, prevention, or inhibition", and both are intended to qualify the amount of the each of the subject compounds for use in therapy which will achieve the goal of improvement in the severity of pain and inflammation and the frequency of incidence, while avoiding adverse side effects typically associated with alternative therapies.

[00062] Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711.

[00063] The frequency of dose will depend upon the half-life of the active components of the composition. If the active molecules have a short half life (*e.g.* from about 2 to 10 hours) it may be necessary to give one or more doses per day. Alternatively, if the active molecules have a long half-life (*e.g.* from about 2 to about 15 days) it may only be necessary to give a dosage once per day, per week, or even once every 1 or 2 months. A preferred dosage rate is to administer the dosage amounts described above to a subject once per day.

[00064] For the purposes of calculating and expressing a dosage rate, all dosages that are expressed herein are calculated on an average amount-per-day basis irrespective of the dosage rate. For example, one 100 mg dosage of an aminocyanopyridine MK-2 inhibitor taken once every two days would be expressed as a dosage rate of 50 mg/day. Similarly, the dosage rate of an ingredient where 50 mg is taken twice per day would be expressed as a dosage rate of 100 mg/day.

[00065] For purposes of calculation of dosage amounts, the weight of a normal adult human will be assumed to be 70 kg.

[00066] When the aminocyanopyridine MK-2 inhibitor is supplied along with a pharmaceutically acceptable carrier, the pharmaceutical compositions that are described above can be formed. Pharmaceutically acceptable carriers include, but are not limited to, physiological saline, Ringer's, phosphate solution or buffer, buffered saline, and other carriers known in the art. Pharmaceutical compositions may also include stabilizers, anti-oxidants, colorants, and diluents. Pharmaceutically acceptable carriers and additives are chosen such that side effects from the pharmaceutical compound are minimized and the performance of the compound is not canceled or inhibited to such an extent that treatment is ineffective.

[00067] The term "pharmacologically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician. This amount can be a therapeutically effective amount.

[00068] The term "pharmaceutically acceptable" is used herein to mean that the modified noun is appropriate for use in a pharmaceutical product. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to, appropriate alkali metal salts, alkaline earth metal salts and other physiological acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, *N*,*N*'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (*N*-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include, without limitation, hydrochloric acid, hydroiodic acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

[00069] Also included in the invention are the isomeric forms and tautomers and the pharmaceutically-acceptable salts of the aminocyanopyridine MK-2 inhibitors. Illustrative pharmaceutically acceptable salts are prepared from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic,

cyclohexylaminosulfonic, algenic, β-hydroxybutyric, galactaric and galacturonic acids.

[00070] Suitable pharmaceutically-acceptable base addition salts of compounds of the present invention include metallic ion salts and organic ion salts. More preferred metallic ion salts include, but are not limited to, appropriate alkali metal (Group Ia) salts, alkaline earth metal (Group IIa) salts and other physiological acceptable metal ions. Such salts can be made from the ions of aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from tertiary amines and quaternary ammonium salts, including in part, trifluoroacetate, trimethylamine, diethylamine, *N,N*-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (*N*-methylglucamine) and procaine. All of the above salts can be prepared by those skilled in the art by conventional means from the corresponding compound of the present invention.

[00071] The tricyclic aminocyanopyridine compouds of the present invention are useful for, but not limited to, the prevention and treatment of diseases and disorders that are mediated by TNFα. For example, the aminocyanopyridine MK-2 inhibitors of the invention would be useful to treat arthritis, including, but not limited to, rheumatoid arthritis, spondyloarthopathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. Such aminocyanopyridine MK-2 inhibitor compounds of the invention would be useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, connective tissue injuries or disorders, and skin related conditions such as psoriasis, eczema, burns and dermatitis.

[00072] The tricyclic aminocyanopyridine MK-2 inhibitor compounds that are useful in the method of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, gastric ulcer, gastric varices, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis and for the prevention or treatment of cancer, such as colorectal cancer. Such aminocyanopyridine MK-2 inhibiting compounds

would be useful in treating inflammation in diseases and conditions such as herpes simplex infections, HIV, pulmonary edema, kidney stones, minor injuries, wound healing, vaginitis, candidiasis, lumbar spondylanhrosis, lumbar spondylarthrosis, vascular diseases, migraine headaches, sinus headaches, tension headaches, dental pain, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, swelling occurring after injury, myocardial ischemia, and the like.

[00073] The tricyclic aminocyanopyridine MK-2 inhibitors would also be useful in the treatment of ophthalmic diseases, such as retinitis, retinopathies, conjunctivitis, uveitis, ocular photophobia, and of acute injury to the eye tissue. These compounds would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis. The compounds would also be useful for the treatment of certain central nervous system disorders such as cortical dementias including Alzheimer's disease.

[00074] As used herein, the terms "TNFα mediated disease or disorder" are meant to include, without limitation, each of the symptoms or diseases that is mentioned above.

[00075] The terms "treating" or "to treat" mean to alleviate symptoms, eliminate the causation either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms. The term "treatment" includes alleviation, elimination of causation of or prevention of pain and/or inflammation associated with, but not limited to, any of the diseases or disorders described herein. Besides being useful for human treatment, the present compounds are also useful for treatment of mammals, including horses, dogs, cats, rats, mice, sheep, pigs, etc.

[00076] The term "subject" for purposes of treatment includes any human or animal subject who is in need of the prevention of or treatment of any one of the TNFα mediated diseases or disorders. The subject is

typically a mammal. "Mammal", as that term is used herein, refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cattle, etc., Preferably, the mammal is a human.

[00077] For methods of prevention, the subject is any human or animal subject, and preferably is a subject that is in need of prevention and/or treatment of a TNFα mediated diseases or disorders. The subject may be a human subject who is at risk of obtaining a TNFα mediated disease or disorder, such as those described above. The subject may be at risk due to genetic predisposition, sedentary lifestyle, diet, exposure to disorder-causing agents, exposure to pathogenic agents and the like.

[00078] The subject pharmaceutical compositions may be administered enterally and parenterally. Parenteral administration includes subcutaneous, intramuscular, intradermal, intramammary, intravenous, and other administrative methods known in the art. Enteral administration includes solution, tablets, sustained release capsules, enteric coated capsules, and syrups. When administered, the pharmaceutical composition may be at or near body temperature.

[00079] In particular, the pharmaceutical compositions of the present invention can be administered orally, for example, as tablets, coated tablets, dragees, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate;

granulating and disintegrating agents, for example, maize starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

[00080] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredients are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients are present as such, or mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

[00081] Aqueous suspensions can be produced that contain the aminocyanopyridine MK-2 inhibitors in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone gum tragacanth and gum acacia; dispersing or wetting agents may be naturally-occurring phosphatides, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate.

[00082] The aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate, one or

more coloring agents, one or more flavoring agents, or one or more sweetening agents, such as sucrose or saccharin.

[00083] Oily suspensions may be formulated by suspending the active ingredients in an omega-3 fatty acid, a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol.

[00084] Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

[00085] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[00086] Syrups and elixirs containing the novel MK-2 inhibitors may be formulated with sweetening agents, for example glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

[00087] The subject compositions can also be administered parenterally, either subcutaneously, or intravenously, or intramuscularly, or intrasternally, or by infusion techniques, in the form of sterile injectable aqueous or olagenous suspensions. Such suspensions may be formulated according to the known art using those suitable dispersing of wetting agents and suspending agents which have been mentioned above, or other acceptable agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are

water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono-, or di-, glycerides. In addition, n-3 polyunsaturated fatty acids may find use in the preparation of injectables.

[00088] The subject compositions can also be administered by inhalation, in the form of aerosols or solutions for nebulizers, or rectally, in the form of suppositories prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperature but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and poly-ethylene glycols.

[00089] The novel compositions can also be administered topically, in the form of creams, ointments, jellies, collyriums, solutions or suspensions.

[00090] Daily dosages can vary within wide limits and will be adjusted to the individual requirements in each particular case. In general, for administration to adults, an appropriate daily dosage has been described above, although the limits that were identified as being preferred may be exceeded if expedient. The daily dosage can be administered as a single dosage or in divided dosages.

[00091] Various delivery systems include capsules, tablets, and gelatin capsules, for example.

[00092] The following examples describe preferred embodiments of the invention. Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from consideration of the specification or practice of the invention as disclosed herein. It is intended that the specification, together with the examples, be considered to be exemplary only, with the scope and spirit of the invention being indicated by the claims which follow the examples. In the examples all percentages are given on a weight basis unless otherwise indicated.

GENERAL INFORMATION FOR PREPARATION METHODS:

[00093] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers.

[00094] NMR analysis:

[00095] Proton nuclear magnetic resonance spectra were obtained on a Varian Unity Innova 400, a Varian Unity Innova 300 a Varian Unity 300, a Bruker AMX 500 or a Bruker AV-300 spectrometer. Chemical shifts are given in ppm (δ) and coupling constants, *J*, are reported in Hertz. Tetramethylsilane was used as an internal standard for proton spectra and the solvent peak was used as the reference peak for carbon spectra. Mass spectra were obtained on a Perkin Elmer Sciex 100 atmospheric pressure ionization (APCI) mass spectrometer, a Finnigan LCQ Duo LCMS ion trap electrospray ionization (ESI) mass spectrometer, a PerSeptive Biosystems Mariner TOF HPLC-MS (ESI), or a Waters ZQ mass spectrometer (ESI).

[00096] Determination of MK-2 IC_{50}:

[00097] Recombinant MAPKAPK2 was phosphorylated at a concentration of 42-78 μM by incubation with 0.23 μM of active p38α in 50 mM HEPES, 0.1 mM EDTA, 10 mM magnesium acetate, and 0.25 mM ATP, pH 7.5 for one hour at 30°C.

[00098] The phosphorylation of HSP-peptide (KKKALSRQLSVAA) by MAPKAPK2 was measured using an anion exchange resin capture assay method. The reaction was carried out in 50 mM β-glycerolphosphate, 0.04 % BSA, 10 mM magnesium acetate, 2% DMSO and 0.8 mM dithiotheritol, pH 7.5 in the presence of the HSP-peptide with 0.2 μCi [γ^{33}P]ATP and 0.03mM ATP. The reaction was initiated by the addition of 15 nM MAPKAPK2 and was allowed to incubate at 30ºC for 30 min. The reaction was terminated and [γ^{33}P]ATP was removed from solution by the addition of 150 μl of AG 1X8 ion exchange resin in 900 mM sodium formate pH 3.0. A 50 μl aliquot of head volume was removed from the quenched reaction mixture and added to a 96-well plate, 150 μl of Microscint-40 (Packard) was added and the amount of phosphorylated-peptide was determined. Allow the Microscint to sit in the plates for 60 minutes prior to counting.

[00099] Compounds are evaluated as potential inhibitors of the MK2 kinase by measuring their effects on MK2 phosphorylation of the peptide substrate. Compounds may be screened initially at two concentrations prior to determination of IC_{50} values. Screening results are expressed as percent inhibition at the concentrations of compound tested. For IC_{50} value determinations, compounds are tested at six concentrations in ten-fold serial dilutions with each concentration tested in triplicate. Results are expressed as IC_{50} values in micromolar. The assay is performed at a final concentration of 2% DMSO.

[000100] Preferred aminocyanopyridine MK-2 inhibiting compounds of the present invention provide IC_{50} values for MK-2 inhibition of below 200 μM. One method that can be used for determining the MK-2 inhibition IC_{50} value is that described just above. More preferred aminocyanopyridine MK-2 inhibiting compounds have the capability of providing MK-2 inhibition IC_{50} values of below 100 μM, yet more preferred of below 50 μM, even more preferred of below 20 μM, yet more preferred of below 10 μM, and even more preferred of below 1μM.

U937 Cell TNFα release assay

[000101] The human monocyte-like cell line, U937 (ATCC #CRL-1593.2), is cultured in RPMI1640 media with 10% heat-inactivated fetal calf serum (GIBCO), glutamine and pen/strep at 37°C and 5% CO_2. Differentiation of U937 to monocytic/macrophage-like cells is induced by the addition of phorbol12-myristate 13-acetate (Sigma) at final concentration of 20 ng/ml to a culture of U937 cells at ~0.5 million cells/ml and incubated for 24 hrs. The cells are centrifuged, washed with PBS and resuspended in fresh media without PMA and incubated for 24 hrs. Cells adherent to the culture flask are harvested by scraping, centrifugation, and resuspended in fresh media to 2 million cells/ml, and 0.2 ml is aliquoted to each of 96 wells in flat-bottom plate. Cells are then incubated for an additional 24 hrs to allow for recovery. The media is removed from the cells, and 0.1 ml of fresh media is added per well. 0.05 ml of serially diluted compound or control

vehicle (Media with DMSO) is added to the cells. The final DMSO concentration does not exceed 1%. After 1hr incubation, 0.05 ml of 400ng/ml LPS (E Coli serotype 0111:B4, Sigma) in media is added for final concentration of 100 ng/ml. Cells are incubated at 37°C for 4 hrs. After 4hrs incubation, supernatants are harvest and assayed by ELISA for the presence of TNFα.

[000102] U937 cell TNFα ELISA

[000103] ELISA plates (NUNC-Immuno™ Plate Maxisorb™ Surface) were coated with purified mouse monoclonal IgG1 anti-human TNFα antibody (R&D Systems #MAB610; 1.25 ug/ml in sodium bicarbonate pH 8.0, 0.1 ml/well) and incubated at 4°C. Coating solution was aspirated the following day and wells were blocked with 1 mg/ml gelatin in PBS (plus 1x thimerasol) for 2 days at 4°C. Prior to using, wells were washed 3x with wash buffer (PBS with 0.05% Tween). Cultured media samples were diluted in EIA buffer (5 mg/ml bovine γ-globulin, 1 mg/ml gelatin, 1 ml/l Tween-20, 1 mg/ml thimerasol in PBS), added to wells (0.1 ml/well) in triplicate and allowed to incubate for 1.5 hr at 37°C in a humidified chamber. Plates were again washed and 0.1 ml/well of a mixture of rabbit anti-human TNFα polyclonal antibodies in EIA buffer (1:400 dilution of Sigma #T8300, and 1:400 dilution of Calbiochem #654250) was added for 1 hr at 37°C. Plates were washed as before and peroxidase-conjugated goat anti-rabbit IgG (H+L) antibody (Jackson ImmunoResearch #111-035-144, 1 ug/ml in EIA buffer, 0.1 ml/well) was added for 45 min. After final washing, plates were developed with peroxidase-ABTS solution (Kirkegaard/Perry #50-66-01, 0.1 ml/well). Enzymatic conversion of ABTS to colored product was measured after 5-30 minutes using a SpectroMax 340 spectrophotometer (Molecular Devices) at 405 nm. TNF levels were quantitated from a recombinant human TNFα (R&D Systems #210-TA-010) standard curve using a quadratic parameter fit generated by SoftMaxPRO software. ELISA sensitivity was approximately 30 pg

TNF/ml. IC_{50} values for compounds were generated using BioAssay Solver.

[000104] Preferred aminocyanopyridine MK-2 inhibiting compounds of the present invention provide TNFα release IC_{50} values of below 200 μM in an *in vitro* cell assay. One method that can be used for determining TNFα release IC_{50} in an *in vitro* cell assay is that described just above. More preferred aminocyanopyridine MK-2 inhibiting compounds have the capability of providing TNFα release IC_{50} values of below 50 μM, yet more preferred of below 10, and even more preferred of below 1.0 μM.

[000105] Lipopolysaccharide (LPS)-Induced TNFα Production.

[000106] Adult male 225-250 gram Lewis rats (Harlan Sprague-Dawley) were used. Rats were fasted 18 hr prior to oral dosing, and allowed free access to water throughout the experiment. Each treatment group consisted of 5 animals.

[000107] Compounds were prepared as a suspension in a vehicle consisting of 0.5% methylcellulose, 0.025% Tween-20 in PBS. Compounds or vehicle were orally administered in a volume of 1 ml using an 18 gauge gavage needle. LPS (E. coli serotype 0111:B4, Lot #39H4103, Cat. # L-2630, Sigma) was administered 1-4 hr later by injection into the penile vein at a dose of 1 mg/kg in 0.5 ml sterile saline. Blood was collected in serum separator tubes via cardiac puncture 1.5 hr after LPS injection, a time point corresponding to maximal TNFα production. After clotting, serum was withdrawn and stored at -20°C until assay by ELISA (described below).

[000108] Rat LPS TNFα ELISA

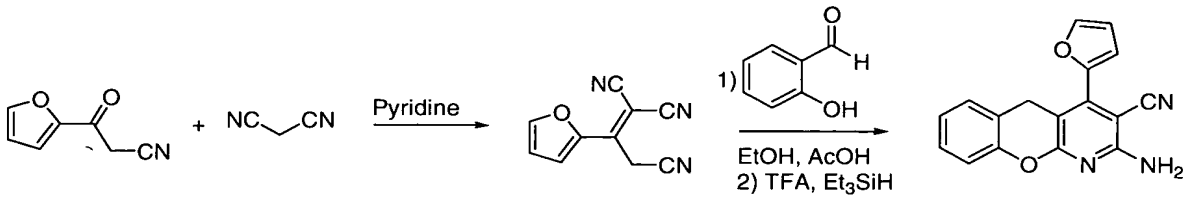
[000109] ELISA plates (NUNC-Immuno™ Plate Maxisorb™ Surface) were coated with 0.1 ml per well of an Protein G purified fraction of a 2.5 ug/ml of hamster anti-mouse/rat TNFα monoclonal antibody TN19.12 (2.5 ug/ml in PBS, 0.1 ml/well). The hybridoma cell line was kindly provided by Dr. Robert Schreiber, Washington University. Wells were blocked the following day with 1 mg/ml gelatin in PBS. Serum samples were diluted in

a buffer consisting of 5 mg/ml bovine γ-globulin, 1 mg/ml gelatin, 1 ml/l Tween-20, 1 mg/ml thimerasol in PBS, and 0.1 ml of diluted serum was added wells in duplicate and allowed to incubate for 2 hr at 37°C. Plates were washed with PBS-Tween, and 0.1 ml per well of a 1:300 dilution of rabbit anti-mouse/rat TNFα antibody (BioSource International, Cat. #AMC3012) was added for 1.5 hr at 37°C. Plates were washed, and a 1:1000 fold dilution of peroxidase-conjugated donkey anti-rabbit IgG antibody (Jackson ImmunoResearch, Cat. #711-035-152) was added for 45 min. After washing, plates were developed with 0.1 ml of ABTS-peroxide solution (Kirkegaard/Perry, Cat. #50-66-01). Enzymatic conversion of ABTS to colored product was measured after ~30 minutes using a SpectroMax 340 spectrophotometer (Molecular Devices Corp.) at 405 nm. TNF levels in serum were quantitated from a recombinant rat TNFα (BioSource International, Cat. #PRC3014.) standard curve using a quadratic parameter fit generated by SoftMaxPRO software. ELISA sensitivity was approximately 30 pg TNF/ml. Results are expressed in percent inhibition of the production of TNFα as compared to blood collected from control animals dosed only with vehicle.

[000110] Preferred aminocyanopyridine MK-2 inhibiting compounds of the present invention are capable of providing some degree of inhibition of TNFα in animals. That is, the degree of inhibition of TNFα in animals is over 0%. One method for determining the degree of inhibition of TNFα is the rat LPS assay that is described just above. More preferred aminocyanopyridine MK-2 inhibiting compounds have the capability of providing rat LPS TNFα inhibition values of at least about 25%, even more preferred of above 50%, yet more preferred of above 70%, and even more preferred of above 80%.

EXAMPLE 1

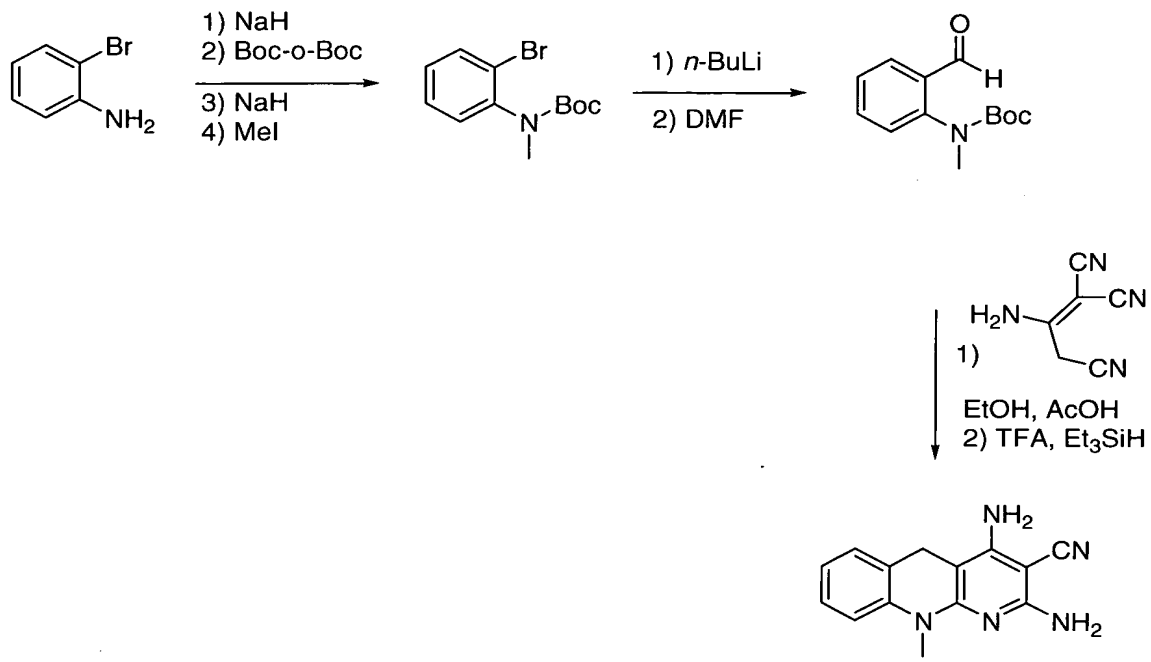
[000111] This illustrates the production of 2-amino-4-(2-furyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile.



[000112] 3-(2-furyl)-3-oxopropanenitrile (10 mmol, 1.0 equiv., 1.35g) and malononitrile (10 mmol, 1.0 equiv., 600μL) were combined in pridine (10mL). The mixture was heated to 100 °C for 1 hour. The reaction mixture was diluted with 150 mL dichloromethane and washed with 1 M hydrochloric acid (HCl) (3 x 50 mL). The organic layer was dried and evaporated to give a dark oil. The oil was dissolved in ethyl alcohol (EtOH) (30 mL) and treated with salicaldehyde (10 mmol, 1.0 equiv., 1.0 mL) and acetic acid (AcOH) (10 mL). The resulting mixture was heated to reflux for 2 hours. The solvents were evaporated and the *in vacuo* and the residue was dissolved in trifluoroacetic acid (15mL). Triethylsilane (10 mL) was added and the solution was stirred overnight. The solvents were evaporated and the residue purified by reverse phase chromatography. The product was isolated as a solid (370mg, 13%). ^{1}H NMR (400 MHz, DMSO) δ 7.99 (s, 1H), 7.24-7.20 (m, 2H), 7.08-7.04 (m, 3H), 6.94 (bs, 2H), 6.76 (s, 1H), 3.96 (s, 2H): m/z 290 (M+H).

EXAMPLE 2

[000113] This illustrates the production of 2,4-diamino-10-methyl-5,10-dihydrobenzo[b]-1,8-naphthyridine-3-carbonitrile trifluoroacetate.

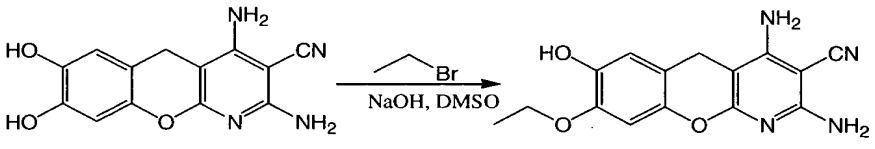


[000114] Step A: (synthesis of *t*-Butyl 2-bromophenyl(methyl)carbamate) 2-bromoaniline (25 mmol, 1.0 equiv. 4.3g) was dissolved in tetrahydrofuran (THF) (150 mL). Sodium hydride (60% in mineral oil, 1.1g) was added and the mixture heated to reflux for 1 hour. After cooling to room temperature, a solution of di-*t*-butyl-dicarbonate in THF (1.0M, 30 mmol, 1.2 equiv., 30 mL) was added followed by sodium hydride (1.1g). The resulting mixture was heated to reflux for 14 hours. After cooling to room temperature, Iodomethane (28 mmol, 1.12 equiv., 1.75 mL) was added and the mixture heated to reflux for 3 hours. After cooling to room temperature, the reaction was quenched with water and diluted with ether. The organic layer was washed with saturated aqueous ammonium chloride (sat. aq. NH_4Cl), saturated aqueous sodium bicarbonate (sat. aq. $NaHCO_3$), and saturated aqueous sodium chloride (sat. aq. NaCl). The organic layer was dried over magnesium sulfate ($MgSO_4$), filtered and evaporated to give a yellow oil. Purification by silica gel chromatography gave the product as a yellow oil (5.9g, 82%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 1H), 7.29 (t, 1H), 7.21 (d, 1H), 7.12 (t, 1H), 3.13 (s, 3H), 1.33 (s, 9H): m/z 271 (M+H).

[000115] Step B: (synthesis of 2,4-diamino-10-methyl-5,10-dihydrobenzo[b]-1,8-naphthyridine-3-carbonitrile trifluoroacetate)*t*-Butyl 2-bromophenyl(methyl)carbamate (2.65 mmol, 1.0 equiv., 759 mg) was dissolved in THF (20 mL). The solution was cooled in a dry ice acetone bath and a solution of *n*-BuLi in hexane (1.6M, 1.1 equiv. 1.8 mL) was added dropwise. After 15 minutes, dimethylformamide (DMF) (1 mL) was added and the reaction allowed to warm to room temperature. The reaction mixture was quenched with sat. aq. NH_4Cl, and partitioned between ether and water. The organic layer was washed with water and dried over $MgSO_4$, filtered and evaporated to get 820 mg of a yellow oil. This oil was carried on immediately without purification or characterization. The resulting oil was treated with 2-amino-1-propene-1,1,3-tricarbonitrile (2 mmol, 265mg), acetic acid (2.0mL), and ethanol (10mL) and the resulting solution was heated to reflux overnight. The reaction slurry was concentrated *in vacuo* and then dissolved in trifluoroacetic acid (TFA) (7mL) at 0°C. Triethylsilane (5.0mL) was added via syringe. The reaction stirred for 2 hours before evaporating solvents to get a brown solid. The solid was washed with dichloromethane and dried to give the product as a light brown solid. (90mg, 9%). ^1H NMR (400 MHz, DMSO) δ 7.16 (t, 1H), 7.03 (d, 1H), 6.97-6.91 (m, 2H), 3.70 (s, 2H), 3.34 (s, 3H): m/z 252 (M+H).

EXAMPLE 3

[000116] This illustrates the production of 2,4-diamino-8-ethoxy-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.



[000117] 2,4-diamino-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile (400 mg, 1.0 mmol) and sodium hydroxide (NaOH) (166 mg, 4.2 mmol) were suspended in simethylsulfoxide (DMSO) (5 mL) and warmed until dissolved. Ethyl bromide was added to the reaction mixture,

which was heated to 85°C until disappearance of starting material (HPCL monitoring). After neutralizing with NH_4Cl, the crude reaction mixture was purified by reverse phase column chromatography (gradient of acetonitrile, H_2O, 0.05% TFA). Evaporation of the solvent on a lyophilizer gave an orange solid as a TFA salt 2,4-diamino-8-ethoxy-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile, which was confirmed by 2D NMR analysis. ^1H NMR (300 MHz, CD3OD): δ 1.47 (t, 3H), 3.63 (s, 2H), 4.12 (quartet, 2H), 6.59-6.81 (m, 2H). HRMS calcd for C15H14N4O3 (M+H): 299.11. Found: 299.1132.

EXAMPLE 4

[000118] This illustrates the production of 2,4-diamino-8-(2-ethoxyethoxy)-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000119] 2,4-diamino-8-(2-ethoxyethoxy)-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared from 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile in the same method as described above in Example 3, using 2-bromoethyl-ethylether in lieu of 2-bromoethyl-ethylether. ^1H NMR (300 MHz, CD3OD): δ 1.28 (t, 3H), 3.60 (s, 2H), 3.67 (quartet, 2H), 3.86 (s, 2H), 4.19 (s, 2H), 6.58-6.82 (m, 2H). HRMS calcd for C17H18N4O4 (M+H): 343.13. Found: 343.1418.

EXAMPLES 5 - 6

[000120] This illustrates the production of aminocyanopyridine compounds of the present invention.

[000121] The aminocyanopyridine compounds shown in the table below were prepared according to the general method described in Example 3. NMR analysis was carried out according to the method described above, and resulting data for each of the compounds is provided in the table.

Ex. No.	Compound nam	HRMS calcd	HRMS found
5	tert-butyl {[2,4-diamino-7-(2-tert-butoxy-2-oxoethoxy)-3-cyano-5H-chromeno[2,3-b]pyridin-8-yl]oxy}acetate trifluoroacetate	499.21	499.2204
6	7,8-bis(allyloxy)-2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	351.14	351.1445

EXAMPLE 7

[000122] This illustrates the production of 2,4-diamino-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000123] To a cooled (0 °C) solution of 2,4-diamino-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile (1.34mmol, 400mg) and dichloromethane (4.0mL) was slowly added boron tribromide (1M, dichloromethane, 8.04mmol, 8.04mL). The suspension was stirred at 0 °C for 15 minutes, then the ice bath was removed and the reaction warmed to 23 °C overnight. After 16h at 23 °C the reaction was cooled to 0°C and carefully neutralized with 2.5N sodium hydroxide to pH = 7. The product was collected by filtration, dissolved in dimethyl sulfoxide (1.0 mL) and purified by reverse phase chromatography. The product was isolated as a pale orange solid (62mg, 17% yield). ^{1}H NMR (400 MHz, DMSO) δ 9.071(s, 1H), 8.795 (s, 1H), 6.520 (s, 1H), 6.410 (bs, 2H), 6.405(s, 1H), 6.244 (bs, 2H), 3.48 (s, 2H): m/z 271 (M+); HRMS (M+H) calculated for $C_{13}H_{11}N_4O_3$ 271.0753, found 271.0721.

EXAMPLE 8

[000124] This illustrates the production of 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000125] 2,4-Dihydroxy-benzaldehyde (43.4mmol, 6.0g), 2-amino-1-propene-1,1,3-tricarbonitrile (43.4mmol, 5.74g), acetic acid (13.0mL), and ethanol (125.0mL) were combined and heated to reflux for 2 hours. The reaction slurry was concentrated *in vacuo* and then dissolved in trifluoroacetic acid (160.0mL) at 0°C. Triethylsilane (0.28mol, 32.76g, 45.0mL) was added via syringe. The reaction was stirred for 1 hour at 0°C. 300mL of dichloromethane was added to the reaction and the solid was collected via filtration and washed (2x75mL) with dichloromethane and ether. The product was isolated as a pale orange solid (13.10g, 63% yield). ^{1}H NMR (400 MHz, DMSO) δ 6.958(d, 1H), 6.537 (dd, 1H), 6.390 (d, 1H), 3.510(s, 2H): m/z 255 (M+); HRMS (M+H) calculated for $C_{13}H_{11}N_4O_2$ 255.0804, found 255.0894.

EXAMPLE 9

[000126] This illustrates the production of 8,10-diamino-2,3-dihydro-11H-[1,4]dioxino[2',3':6,7]chromeno[2,3-b]pyridine-9-carbonitrile.

[000127] 2,4-diamino-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile (0.56mmol, 150mg) was dissolved in DMSO (3.0mL) and sodium hydroxide (2.24mmol, 90mg) was added followed by dibromoethane (0.56mmol, 105.20mg, 48.26μL). The dark homogeneous solution was heated to 70°C for 16 hours. The crude reaction mixture was cooled to 23°C, neutralized with trifluoroacetic acid and directly purified via reverse phase chromatography. The product was isolated as a pale orange solid (30mg, 18% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 6.715(s, 1H), 6.553 (s, 1H), 4.215 (bs, 4H), 3.575(s, 2H): m/z 298 (M+H).

EXAMPLE 10

[000128] This illustrates the production of 2,4-diamino-8-(2-ethoxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000129] 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile (0.62mmol, 300mg) was dissolved in DMSO (4.0mL) and solid sodium hydroxide (2.79mmol, 111.6mg) was added followed by 2-bromoethyl-ethylether (0.62mmol, 69.9μL). The reaction was heated to

80°C with stirring for 9 hours. The crude reaction was filtered and diluted with DMSO (4.0mL) and purified via reverse phase chromatography. The product was isolated as a tan solid (80mg, 40% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.180(d, 1H), 6.795 (d, 1H), 6.46 (d, 1H), 4.090 (t, 2H), 3.766(t, 2H), 3.607 (s, 2H), 3.572 (t, 2H), 1.200 (t, 2H); m/z 327 (M+H).

EXAMPLE 11

[000130] This illustrates the production of 2,4-diamino-8-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile .

[000131] 2,4-diamino-8-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared from 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrilein the same manner as described in Example 10, using 1-(2-chloroethyl)pyridine in lieu of 2-bromoethyl-ethylether. The product was isolated as a tan solid (100mg, 46% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.199 (d, 1H), 6.680 (d, 1H), 6.668 (d, 1H), 4.290 (t, 2H), 3.618 (s, 2H), 3.562 (t, 2H), 3.375 (bs, 4H), 2.077(bs, 4H); m/z 352 (M+H). TNFα release assay IC_{50}: 2.9μM; Rat LPS Assay 60% inhibition at 20 mpk (IP).

EXAMPLE 12

[000132] This illustrates the production of 2,4-diamino-8-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000133] 2,4-diamino-8-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared from 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile in the same manner as described in Example 10 using 2-bromoethylamine in lieu of 2-bromoethyl-ethylether. The product was isolated as a tan solid (167mg, 51% yield). ^{1}H NMR (400 MHz, DMSO) δ 8.180 (bs, 2H), 7.100 (d, 1H), 6.762 (d, 1H), 6.646 (bs, 1H), 4.154 (t, 2H), 3.573 (s, 2H), 3.155 (t, 2H); m/z 398 (M+H). TNFα release assay IC_{50}: 6.9μM; Rat LPS Assay 88% inhibition at 20 mpk (IP).

EXAMPLE 13

[000134] This illustrates the production of [(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-8-yl)oxy]acetic acid.

[000135] [(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-8-yl)oxy]acetic acid was prepared from 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile in the same manner as described in Example 10 using bromoacetic acid in lieu of 2-bromoethyl-ethylether. The product was isolated as a tan solid (110.6mg, 31% yield). ^{1}H NMR (400 MHz, DMSO) δ 7.030 (d, 1H), 6.640 (d, 1H), 6.516 (d, 1H), 6.474 (bs, 2H), 6.278 (bs, 2H), 4.633 (s, 2H), 3.543 (s, 2H); m/z 427 (M+H).

EXAMPLE 14

[000136] This illustrates the production of 2,4-diamino-8-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000137] 2,4-diamino-8-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared from 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile in the same manner as described in Example 10 using 2-bromoethanol in lieu of 2-bromoethyl-ethylether. The product was isolated as a tan solid (120mg, 35% yield). ^{1}H NMR (400 MHz, DMSO) δ 7.025 (d, 1H), 6.670 (d, 1H), 6.550 (d, 1H), 3.931 (t, 2H), 3.662 (t, 2H), 3.546 (s, 2H); m/z 413 (M+H).

EXAMPLE 15

[000138] This illustrates the production of 2,4-diamino-8-(2-morpholin-4-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000139] 2,4-diamino-8-(2-morpholin-4-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared from 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile in the same manner as described in Example 10 using 1-(2-chloroethyl)morpholine in lieu of 2-bromoethyl-ethylether. The product was isolated as a tan solid (80mg, 17% yield). ^{1}H NMR (400 MHz, DMSO) δ 7.071 (d, 1H), 6.714 (d, 1H), 6.654 (d, 1H), 6.527 (bs, 2H), 6.323 (bs, 2H), 4.311 (t, 2H), 3.938 (m, 2H), 3.664 (t, 2H), 3.558 (s, 2H), 3.534 (m, 2H), 3.451 (m, 2H), 3.158 (m, 2H); m/z 482 (M+H).

EXAMPLES 16 - 22

[000140] This illustrates the production of aminocyanopyridine compounds of the present invention.

[000141] The aminocyanopyridine compounds shown in the table below were prepared according to the general method described in Example 10. NMR analysis was carried out according to the method described above, and resulting data for each of the compounds is provided in the table.

Ex. No.	Compound name	m/z (M+H)
16	2,4-diamino-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	269
17	7,9-diamino-10H-[1,3]dioxolo[6,7]chromeno[2,3-b]pyridine-8-carbonitrile	283
18	8-(allyloxy)-2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	295
19	2-amino-8-ethoxy-4-(ethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	311
20	8-ethoxy-2,4-bis(ethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	339
21	2-amino-8-(2-ethoxyethoxy)-4-[(2-ethoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	399
22	2,4-diamino-8-[2-(dimethylamino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	326

EXAMPLE 23

[000142] This illustrates the production of 2,4-diamino-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile bis(trifluoroacetate).

[000143] 3-Methoxysalicyaldehyde (10 mmol, 1.52 g), 2-amino-1-propene-1,1,3-tricarbonitrile (10 mmol, 1.32 g) acetic acid (2.5 mL), and ethanol (40 mL) were combined and heated to reflux overnight. The reaction slurry was concentrated *in vacuo* and then dissolved in trifluoroacetic acid (15 mL) at 0°C. Triethylsilane (62 mmol, 7.2 g, 10 mL) was added via syringe. The reaction stirred for one hour at room temperature. Dichloromethane (100 mL) was added to the reaction and the solid formed was collected via filtration and washed with dichloromethane (2x). The product was isolated as a white solid (2.5 g, 50% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.08 (t, J = 8Hz,1H), 7.00-

6.80 (m, 2H), 6.73 (d, J = 7.4 Hz, 2H), 3.83(s, 3H), 3.68 (s, 2H); m/z 269 (M+H); Anal. calculated for $C_{14}H_{12}N_4O_2$-2CF_3CO_2H: C, 43.56; H, 2.84; N, 11.29, found: C, 43.40; H, 2.98; N, 11.32.

EXAMPLE 24

[000144] This illustrates the production of 2,4-diamino-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate.

[000145] 2,4-diamino-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared in the same manner as described in Example 23, except that 5-hydroxysalicyaldehyde was used in place of methoxysalicyaldehyde. The product was isolated as a pink solid (951 mg, 30% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.88 (d, J = 8.8 Hz, 1H), 6.63 (d, J=8.7 Hz, 1H), 6.55(s, 1H), 3.6 (s, 2H): m/z 255 (M+H); Anal. calculated for $C_{13}H_{10}N_4O_2$-1.5CF_3CO_2H -0.5H_2O: C, 44.25; H, 2.90; N, 12.90, found: C, 44.04; H, 3.05; N, 12.84.

EXAMPLE 25

[000146] This illustrates the production of 2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile Bis(trifluoroacetate).

[000147] 2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared in the same manner as described in Example 23 except that salicyaldehyde was used in place of methoxysalicyaldehyde. The product was isolated as a light tan solid (1.26 g, 33% yield). ^{1}H NMR (300 MHz, DMSO-d_6), δ 7.30-6.90 (m, 6H), 3.7 (s, 2H); m/z 239 (M+H); Anal. Calcd for $C_{13}H_{10}N_4O$-2CF_3CO_2H -0.25H_2O: C, 43.37; H, 2.68; N, 11.90, found: C, 43.07; H, 2.81; N, 11.79.

EXAMPLE 26

[000148] This illustrates the production of 2,4-diamino-8,9-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate.

[000149] 2,4-diamino-8,9-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared in the same manner as described in Example 23, except that 2,3,4-trihydroxybenzaldehyde was used in place of methoxysalicyaldehyde. The product was isolated as a white solid (3.6 g,

82% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.1 (bs, 3H), 6.58 (d, J = 8 Hz, 1H), 6.47 (d, J = 8 Hz, 1H), 3.75 (s, 2H); m/z 271(M+H).

EXAMPLE 27

[000150] This illustrates the production of 2,4-diamino-9-hydroxy-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate.

[000151] 2,3-dihydroxy-4-methoxybenzaldehyde (3 mmol, 506 mg), 2-amino-1-propene-1,1,3-tricarbonitrile (3 mmol, 398 mg), acetic acid (1 mL), and ethanol (15 mL) were combined and heated to reflux overnight. The reaction slurry was concentrated *in vacuo* and then dissolved in trifluoroacetic acid (10 mL) at 0°C. Triethylsilane (25 mmol, 2.88 g, 4 mL) was added via syringe. The reaction stirred for overnight at room temperature to give a yellow slurry. Dichloromethane (50 mL) was added to the reaction and the solid formed was collected via filtration and washed with dichloromethane (2x). The product was isolated as a yellow solid (482 mg, 35% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.73 (d, J=8.5 Hz, 1H), 6.57 (d, J=8.5 Hz,1H), 3.77(s, 3H), 3.57 (s, 2H); m/z 285 (M+H); Anal. calculated for $C_{14}H_{12}N_4O_3$-1.25CF_3CO_2H -1.5H_2O: C, 43.58; H, 3.62; N, 12.32, found: C, 43.80; H, 3.22; N, 12.65.

EXAMPLE 28

[000152] This illustrates the production of 2,4-diamino-9-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate.

[000153] 2,3-dihydroxybenzaldehyde (5 mmol, 691 mg), 2-amino-1-propene-1,1,3-tricarbonitrile (5 mmol, 661 mg), acetic acid (1.2 mL), and ethanol (20 mL) were combined and heated to reflux overnight. The reaction slurry was concentrated *in vacuo* and then dissolved in trifluoroacetic acid (20 mL) at 0°C. Triethylsilane (62 mmol, 7.2 g, 10 mL) was added via syringe. The reaction stirred for two and one-half days at room temperature to give a solution, which was concentrated *in vacuo*. The residue was stirred in methanol and the slurry was filtered. The product was obtained as a brown solid by concentrating the filtrate (167 mg, 9% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.91 (t, J = 7.7 Hz, 1H), 6.86-6.70 (m, 2H), 6.59 (d, J = 7.3 Hz 1H), 3.61 (s, 2H); m/z 255 (M+H).

EXAMPLE 29

[000154] This illustrates the production of 2,4,7-triamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000155] Step A: Preparation of 2,4-diamino-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile: 5-nitrosalicylaldehyde (132 mmol, 22.00 g), 2-amino-1-propene-1,1,3-tricarbonitrile (132 mmol, 17.39 g), acetic acid (31 mL), and ethanol (500 mL) were combined and heated to reflux overnight. The resulting slurry was concentrated *in vacuo* and then dissolved in trifluoroacetic acid (350 mL) at 0°C. Triethylsilane (1.40 mol, 162 g, 225 mL) was added. The mixture was heated overnight at 66 °C. The mixture was cooled and concentrated *in vacuo*. Triturating with methanol gave 2,4-diamino-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile as a yellow solid (22.48 g, 60%yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.13 (d, J = 9.0 Hz, 1H), 8.00 (s, 1H), 7.25 (d, J = 9.0 Hz, 1H), 6.70 (br s, 2H), 6.50 (bs, 2H), 3.82 (s, 2H); m/z 284 (M+H); Anal. Calcd for $C_{13}H_9N_5O_3$-0.5H_2O: C, 53.43; H, 3.45; N, 23.96, found: C, 53.41; H, 3.17; N, 23.71.

[000156] Step B: A mixture of 2,4-diamino-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile, produced as described above, (0.55 mmol, 155 mg) and palladium over carbon (Pd/C) (35 mg, 10% on activated carbon) in dimethylformamide (DMF) (15 mL) was stirred under an atmosphere of hydrogen (balloon) for 3.5 hours. The catalyst was removed by filtration using a plug of celite. The filtrated was concentrated *in vacuo* and the residue was triturated with methanol to give 2,4,7-triamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile as a grey solid (109 mg, 79% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.72 (d, J = 8.0 Hz, 1H), 6.39-6.5(m, 4H), 6.25 (s, 2H), 3.52 (s, 2H); m/z 254 (M+H).

EXAMPLE 30

[000157] This illustrates the production of 2,4-diamino-9-fluoro-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate.

[000158] 3-Fluoro-2-hydroxybenzaldehyde (3.45 mmol, 484 mg), 2-amino-1-propene-1,1,3-tricarbonitrile (3.50 mmol, 463 mg), acetic acid (0.9 mL) and ethanol (27 mL) were combined and heated to reflux for 14 hours.

The reaction slurry was concentrated *in vacuo* and then dissolved in trifluoroacetic acid (10.5 mL). Triethylsilane (43mmol, 4.97 g, 6.9 mL) was added via syringe. The reaction was heated to reflux for 5 hours. Dichloromethane (50 mL) was added to the reaction and the solid formed was collected via filtration and washed with methanol. The product was isolated as a white solid (377 mg, 30% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.25-7.19 (m, 1H), 7.15-7.08 (m, 1H), 7.00-6.96 (m, 1H), 6.70 (bs, 2H), 6.51 (bs, 2H), 3.75 (S, 2H); m/z 257 (M+H).

EXAMPLE 31

[000159] This illustrates the production of 2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-7-carboxylic acid Bis(trifluoroacetate).

[000160] 5-Carboxysalicyaldehyde (3 mmol, 500 mg), 2-amino-1-propene-1,1,3-tricarbonitrile (3 mmol, 396 mg) acetic acid (1.2 mL), and ethanol (15 mL) were combined and heated to reflux for 2.5days. The reaction slurry was concentrated *in vacuo* and then dissolved in trifluoroacetic acid (10 mL). Triethylsilane (62 mmol, 7.2g, 10 mL) was added via syringe. The reaction was stirred for 4 hours at 50 °C and then was stirred overnight at room temperature. Dichloromethane (20 mL) was added to the reaction and the solid formed was collected via filtration and washed with dichloromethane (2x). The product was isolated as a yellow solid (560 mg, 36% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.86 (d, J = 7.4 Hz, 1H), 7.85 (s, 1H), 7.31 (d, J = 7.4 Hz, 1H), 6.80 (br s, 2H), 3.85 (s, 2H); m/z 283 (M+H); anal. Calculated for $C_{14}H_{10}N_4O_3$-2CF_3CO_2H-0.25H_2O: C, 42.00; H, 2.45; N, 10.88, found: C, 42.30; H, 2.31; N, 10.51.

EXAMPLE 32

[000161] This illustrates the production of 2,4-diamino-6,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate.

[000162] 2,4-diamino-6,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared in the same manner as described in Example 31, except that 2,4,6-trihydroxybenzaldehyde was used in place of 5-carboxysalicyaldehyde. The product was isolated as an orange solid (106 mg, 9% yield). ^{1}H NMR (free base, 300 MHz, DMSO-d_6): δ 9.65 (s, 1H),

9.40 (s, 1H), 6.41 (s, 2H), 6.35 (s, 2H), 6.10 (s, 1H), 5.85 (s, 1H), 3.31 (s, 2H); m/z 271 (M+H).

EXAMPLES 33 - 51

[000163] This illustrates the production of aminocyanopyridine compounds of the present invention.

[000164] The aminocyanopyridine compounds shown in the table below were prepared according to the general method described in Example 29. NMR analysis was carried out according to the method described above, and resulting data for each of the compounds is provided in the table.

Ex. No.	Compound name	M+H
33	2,4-diamino-7-(dimethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	282
34	2,4-diamino-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile	284
35	2,4-diamino-7-chloro-9-methyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile	287
36	2,4-diamino-6,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	299
37	2,4-diamino-7-(trifluoromethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	323
38	2,4-diamino-7-bromo-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	347
39	2,4-diamino-9-methoxy-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	314
40	2,4-diamino-8-methyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	253
41	2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-9-carboxylic acid bis(trifluoroacetate)	283
42	2,4-diamino-6-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile bis(trifluoroacetate)	269

Ex. No.	Compound name	M+H
43	2,4-diamino-9-bromo-7-chloro-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	351
44	2,4-diamino-6-bromo-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	347
45	2,4,7-triamino-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	284
46	2,4-diamino-9-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile	284
47	2,4,9-triamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	254
48	2,4-diamino-7-fluoro-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	257
49	2,4-diamino-7-chloro-5H-chromeno[2,3-b]pyridine-3-carbonitrile	273
50	2,4-diamino-9-tert-butyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile	295
51	ethyl 2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-9-carboxylate	311

EXAMPLE 52

[000165] This illustrates the production of 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile.

[000166] Step 1: Production of 5-Nitrothiosalicylaldehyde: A mixture of 2-chloro-5-nitrobenzaldehyde (2g, 11 mmol) and lithium sulfide (0.54 g, 11.7 mmol) in 30 mL of anhydrous DMSO was stirred under nitrogen at room temperature overnight. The solution was then added to a mixture of ice-water, acidified with 2N HCl and extracted with ether three times. The combined ether layers were washed with water, brine, dried, filtered and concentrated to give the crude 5-nitro-2-thiosalicylaldehyde as an orange solid (1.3g, 65% yield)

[000167] Step 2: A solution of the crude 5-nitro-2-thiosalicylaldehyde (1.3g, 7.1 mmol), 2-amino-1-propene-1,1,3-tricarbonitrile (7.6 mmol, 1 g), acetic acid (2.5 mL) in 70 mL of ethanol was heated at 76^{0}C under nitrogen overnight. The reaction mixture was cooled to room temperature and filtered. The solid was washed with ethanol to give the desired tricyclic intermediate as a light brown solid (1.5g, 71.4% yield).

[000168] Step 3: A reaction mixture of the aforementioned tricyclic intermediate (1.2 g, 4 mmol) and triethylsilane (15 mL) in 100 mL of trifluoroacetic acid was heated at between 60-65^{0}C under nitrogen for 2 hours. After that, the solution was cooled to room temperature and concentrated in vacuo. Ether was added to the residue. The solid was filtered, washed with additional ether to give 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile as an orange powder (0.9 g, 75% yield). ^{1}H NMR (400 MHz, CD_3CN + D_2O) δ 8.089 (d, 1H), 8.046 (dd, 1H), 7.609 (d, 1H), 3.898 (s, 2H); m/z 300 (M+H).

EXAMPLE 53

[000169] This illustrates the production of 2,4,7-triamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate.

[000170] To 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile (produced as described above in Example 52; 0.8 g, 2.7 mmol) in 9 mL of 50% (by weight) of ethanol-water was added iron powder (0.55 g, 10 mmol). The mixture was heated to 60°C and then 0.5 mL of HCl/ethanol (prepared from 5.2 mL of conc. HCl and 25 mL of 50% of ethanol-water) was added. The resulting mixture was heated at 76°C for 2.5 hours and filtered hot. The solid was washed with 50% ethanol-water. The filtrates were combined and concentrated *in vacuo* to give a brownish yellow solid. The solid was then dissolved in acetonitrile, filtered to remove a small amount of insoluble solid and concentrated *in vacuo*. The resulting solid was then washed with methanol and trifluoroacetic acid. The trifluoroacetic acid filtrate was concentrated in vacuo to give an amber oil. Ether was added and the solid was filtered, washed with ether, air-dried overnight and then dried in a vacuum oven at 44°C for 2 hours to

give the product as a grayish solid (0.53 g, 71% yield). ^{1}H NMR (400 MHz, $CD_3CN + D_2O$) δ 7.153 (d, 1H), 6.792 (s, 1H), 6.698 (d, 1H), 3.628 (s, 2H); m/z 270 (M+H).

EXAMPLE 54

[000171] This illustrates the production of 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide.

[000172] To a solution of 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile, produced as described in Example 52, (3 g, 10 mmol) in 125 mL of trifluoroacetic acid cooled with a water bath was added dropwise 30% hydrogen peroxide (8 g). After addition was completed, the water bath was removed. After 4 hours, additional 30% hydrogen peroxide (2 g) was added and stirring at room temperature was continued for additional 2 hours. After that, water (20 mL) was added and the resulting solution was concentrated to about 70 mL. Then more water was added and the yellow suspension was stirred at room temperature overnight. The suspension was filtered and washed with water to give the desired product as a yellow solid (2 g, 60.4% yield). ^{1}H NMR(400MHz, DMSO + D_2O) δ 8.350 (dd, 1H), 8.265 (d, 1H), 8.220 (d, 1H), 4.160 (s, 2H); m/z 332 (M+H).

EXAMPLE 55

[000173] This illustrates the production of 2,4,7-triamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide.

[000174] A mixture of 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide, produced as described in Example 54, (0.8 g, 2.4 mmol) and iron powder (0.58 g, 10 mmol) in 50% of ethanol-water (10 mL) was heated to 70^{0}C, then 1 mL of HCl/ethanol (prepared from 5.2 mL of conc. HCl and 25 mL of 50% of ethanol-water) was added. The resulting mixture was heated at 76°C for 3 hours and filtered hot. The solid was washed with methanol and trifluoroacetic acid. The trifluoroacetic acid filtrate was concentrated *in vacuo* and ether was added to the viscous oil. The solid was filtered and washed with ether to give the desired product as a beige solid (0.42 g, 57.5% yield). ^{1}H NMR

(400 MHz, DMSO + D_2O) δ 7.521 (d, 1H), 6.60 (dd, 1H), 6.529 (s, 1H), 3.753 (s, 2H); m/z 302 (M+H).

EXAMPLE 56

[000175] This illustrates the production of 2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile.

[000176] 2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile was prepared as a bis-trifluoroacetate in the same manner as described in Example 52, except that 2,5-difluorobenzaldehyde was used as the starting material in place of 2-chloro-5-nitrobenzaldehyde. The product was isolated as a beige solid (0.35 g, 35% yield). ^1H NMR (400 MHz, CD_3CN + D_2O), δ 7.425 (dd, 1H), 7.153 (dd, 1 H), 7.088 (dt, 1H) 3.743 (s, 2H); m/z 273 (M+H)

EXAMPLE 57

[000177] This illustrates the production of 2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile Bis(trifluoroacetate).

[000178] 2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile was prepared in the same manner as described in Example 52, except that 2-fluorobenzaldehyde was used as the starting material in place of 2-chloro-5-nitrobenzaldehyde. The product was isolated as a beige solid (1.8 g, 47.4% yield). ^1H NMR (400 MHz, CD_3CN + D_2O) δ 7.271-7.435 (m, 4H), 3.785 (s, 2 H); m/z 255 (M+H).

EXAMPLE 58

[000179] This illustrates the production of 2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile.

[000180] 2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile was prepared in the same manner as described in Example 52, except that 2-fluoro-5-methoxybenzaldehyde was used as the starting material. The product was isolated as a beige solid (0.5 g, 49% yield). ^1H NMR (400 MHz, CD_3CN + D_2O) δ 7.329 (d, 1H), 6.938 (d, 1H), 6.885 (dd, 1H), 3.795 (s, 3H), 3.710 (s, 2H); m/z 285 (M+H)

EXAMPLE 59

[000181] This illustrates the production of 2,4-diamino-7-hydroxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile.

[000182] A mixture of 2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile (0.3 g, 0.59 mmol), produced as described in Example 58, and 0.6 mL of boron tribromide (6.4 mmol) in 30 mL of methylene chloride was stirred at room temperature for 18 h. After that, the solid was filtered, washed with methylene chloride, water and methanol. The methanol filtrate was concentrated to give a solid, which was washed with water, acetonitrile and ether to give the desired product as a red solid (54 mg, 33.6% yield). ^{1}H NMR (400 MHz, DMSO + D_2O) δ 9.520 (s, 1H), 8.111 (d, 1H), 7.561 (d, 1H), 7.522 (s, 2H); m/z 271 (M+H).

EXAMPLE 60

[000183] This illustrates the production of 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide (an alternative procedure).

[000184] A mixture of 2,4,7-triamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile (0.1 g, 0.26 mmol), produced as described in Example 55, and 30% hydrogen peroxide (1.5 mL) in 3 mL of trifluoroacetic acid was stirred at room temperature overnight. Water (30 mL) was then added and the resulting suspension was stirred at ambient temperature for 2 hours. The solid was filtered to give the desired product as a yellow solid (18 mg, 8.6% yield): ^{1}HNMR (400 MHz, DMSO + D_2O) δ 8.353 (dd, 1H), 8.263 (d, 1H), 8.228 (d, 1H), 4.163 (s, 2H); m/z 332 (M+H).

EXAMPLE 61

[000185] This illustrates the production of 2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide.

[000186] 2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide was prepared in the same manner as 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide, as described in Example 60. The product was isolated as a yellow solid (51 mg, 32.7% yield). ^{1}H NMR (400 MHz, DMSO) δ 8.028 (q, 1H),

7.433 (dt, 1H), 7.253 (d, 1H), 7.162 (bs, 1H), 6.917 (bs, 1H), 4.024 (s, 2H); m/z 305 (M+H).

EXAMPLE 62

[000187] This illustrates the production of 2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide.

[000188] 2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide was prepared in the same manner as 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide, as described in Example 60. The product was isolated as a yellow solid (73 mg, 42.9% yield). ^{1}H NMR (400 MHz, DMSO) δ 7.945 (dd, 1H), 7.762 (dt, 1H), 7.568 (t, 1H), 7.467 (d, 2H), 7.179 (bs, 2H), 6.886 (bs, 1H), 4.009 (s, 2H); m/z 287 (M+H).

EXAMPLE 63

[000189] This illustrates the production of 2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide.

[000190] 2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide was prepared in the same manner as 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide, as described in Example 60. The product was isolated as a light brown solid (110 mg, 34.2% yield). ^{1}H NMR (400 MHz, DMSO + D_2O) δ 7.858 (d, 1H), 7.107 (dd, 1H), 6.972 (d, 1H), 3.942 (2, 2H), 3.833 (s, 3H); m/z 316 (M+H).

EXAMPLES 64 - 65

[000191] This illustrates the production of aminocyanopyridine compounds of the present invention.

[000192] The aminocyanopyridine compounds shown in the table below were prepared according to the general method described in Example 60. NMR analysis was carried out according to the method described above, and resulting data for each of the compounds is provided in the table.

Ex. No.	Compound nam	m/z (M+H)
64	2,4-diamino-9-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	273
65	2,4-diamino-9-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide	305

EXAMPLES 66 - 81

[000193] This illustrates the production of certain aminocyanopyridine compounds of the present invention.

[000194] General procedure for the N-alkylation:

[000195] To a solution of 2,4-diamino-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile (1.34 mmol) and the corresponding halide (2.01 mmol) in dimethylformamide (5 mL) is added sodium hydride (80 mg, 2.01 mmol). The reaction mixture is stirred at room temperature or heated to 40°C until completion. The mixture is quenched with saturated aqueous ammonium chloride and directly purified by purified by reverse phase chromatography. Both the mono alkylated and dialkylated product were isolated.

[000196] The following compounds were prepared using the procedure described above:

Example 66: 2-amino-4-{[2-(dimethylamino)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 67: 2,4-bis{[2-(dimethylamino)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 68: 2-amino-4-[(2-aminoethyl)amino]-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 69: 2-amino-4-{[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 70: 2-amino-7,8-dimethoxy-4-[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 71: 7,8-dimethoxy-2,4-bis[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 72: 2,4-bis(glycinyl)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate,

Example 73: *N*-(2-amino-3-cyano-7,8-dimethoxy-5H-chromeno[2,3-b]pyridin-4-yl)glycine,

Example 74: 7,8-dimethoxy-2,4-bis[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 75: 2-amino-7,8-dimethoxy-4-[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 76: 2,4-bis(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile

Example 77: 2-amino-4-(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 78: 7,8-dimethoxy-2,4-bis(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 79: 2-amino-7,8-dimethoxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 80: 2,4-bis(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile, and

Example 81: 2-amino-4-(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000197] General procedure for the demethylation:

[000198] To a solution of the corresponding dimethoxy aryl analog (0.68 mmol) in dichloromethane (2mL) is slowly added boron tribromide (1M, dichloromethane, 3.38mmol, 3.38mL). The reaction mixture is stirred at room temperature for 4 hours, quenched with 5% aqueous sodium hydroxide, then neutralized with 5% aqueous HCl. The resulting solid is collected and the aqueous layer is extracted with dichloromethane. The organic layer is concentrated under vacuum and combined with the solid. The residue is purified by reverse phase chromatography.

EXAMPLE 82

[000199] This illustrates the production of 2-amino-4-(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000200] 2-amino-4-(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared using the demethylation procedure described above starting with 2-amino-4-(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile. ^{1}H NMR (400 MHz, DMSO) δ 6.5(s, 1H), 6.4 (s, 1H), 3.65(q, 2H), 2.5 (s, 2H), 1.25 (t, 3H); m/z 299.15 (M+H); HRMS (M+H) calculated for $C_{15}H_{15}N_4O_3$ 299.1139, found 299.1113.

EXAMPLE 83

[000201] This illustrates the production of 2-amino-7,8-dihydroxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000202] 2-amino-7,8-dihydroxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile is prepared using the demethylation procedure described above for Examples 66 - 81 starting with 2-amino-7,8-dimethoxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile. ^{1}H NMR (400 MHz, DMSO) δ 6.5(s, 1H), 6.4 (s, 1H), 3.55(m, 2H), 2.5 (s, 2H), 1.6(m, 2H), 1.35 (t, 3H); m/z 313.16 (M+H); HRMS (M+H) calculated for $C_{16}H_{17}N_4O_3$ 313.1295, found 313.1325.

EXAMPLE 84

[000203] This illustrates the production of 2-amino-7,8-dihydroxy-4-[(2-hydroxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000204] 2-amino-7,8-dihydroxy-4-[(2-hydroxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared using the demethylation procedure described above for Examples 66 - 81, starting with 2-amino-7,8-dimethoxy-4-[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile. ^{1}H NMR (400 MHz, DMSO) δ 6.5(s, 1H), 6.4 (s, 1H), 3.65(m, 2H), 3.55(m, 2H), 2.5 (s, 2H); m/z 315.13 (M+H).

EXAMPLE 85

[000205] This illustrates the production of 2,4-bis(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000206] 2,4-bis(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared by using the procedure described in Examples 66 - 81.

EXAMPLES 86 - 91

[000207] This illustrates the production of certain aminocyanopyridine compounds of the present invention.

[000208] General procedure for the O-alkylation of phenol 2,4-diamino-9-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile:

[000209] A solution of 2,4-diamino-9-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile (0.73 mmol), and powdered sodium hydroxide (117 mg, 2.93 mmol)) in dimethyl sulfoxide (4 mL) is heated to 50°C for five minutes. The corresponding halide is added and the reaction mixture is stirred at 50°C or 75°C until completion. The mixture is quenched with saturated aqueous ammonium chloride and directly purified by purified by reverse phase chromatography.

[000210] The following compounds were prepared using the above procedure:

Example 86: 2,4-diamino-9-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 87: (2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-9-yl)oxy]acetic acid,

Example 88: 2,4-diamino-9-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 89: 2,4-diamino-9-[2-(dimethylamino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 90: 2,4-diamino-9-(pyridin-4-ylmethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile, and

Example 91: 2,4-diamino-9-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

EXAMPLES 92 - 120

[000211] This illustrates the production of certain aminocyanopyridine compounds of the present invention.

[000212] General procedure for the Mannich condensation:

[000213] To a solution of the corresponding phenol (0.92 mmol) in ethanol (5 mL) is added formic acid (37% solution, 76 μL, 1.01 mmol) and piperidine (100 μL, 1.01 mmol). The reaction mixture is stirred at 75°C until completion. The mixture is quenched with saturated aqueous ammonium chloride and directly purified by purified by reverse phase chromatography and each regioisomer isolated.

[000214] The following compounds were prepared using the above procedure:

Example 92: 2,4-diamino-9-hydroxy-6,8-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile, and

Example 93: 2,4-diamino-9-hydroxy-8-(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile, were produced starting with 2,4-diamino-9-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile, produced as described in Examples 66 - 81, and

Example 94: 2,4-diamino-8-hydroxy-7,9-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile, was produced starting with 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile, produced as described in Example 8.

[000215] Other aminocyanopyridine compounds of the present invention can be produced by the same general method, and are shown in the table below along with NMR parameters, which were determined as described above.

Ex. No.	Compound name	m/z (M+H)	HRMS Theor.	HRMS Found	Formula Calcd for
95	2,4-diamino-9-hydroxy-8-(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	352.26	352.1768	352.1778	$C_{19}H_{21}N_5O_2$
96	2,4-diamino-8-hydroxy-7,9-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	449.33	449.266	449.2637	$C_{25}H_{32}N_6O_2$
97	2,4-diamino-9-hydroxy-6,8-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	449.32	449.266	449.2629	$C_{25}H_{32}N_6O_2$
98	2,4-diamino-9-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	352.26	352.1768	352.1777	$C_{19}H_{21}N_5O_2$
99	2,4-diamino-9-(pyridin-4-ylmethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	346.16	346.1299	346.1344	$C_{19}H_{15}N_5O_2$
100	2,4-diamino-9-[2-(dimethylamino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	326.24	326.1612	326.1607	$C_{17}H_{19}N_5O_2$
101	2,4-diamino-9-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	299.19	299.1139	299.1153	$C_{15}H_{14}N_4O_3$
102	[(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-9-yl)oxy]acetic acid trifluoroacetate	313.14	313.0931	313.0972	$C_{15}H_{12}N_4O_4$
103	2,4-diamino-9-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	298.18	298.1299	298.1303	$C_{15}H_{15}N_5O_2$

Ex. No.	Compound name	m/z (M+H)	HRMS Theor.	HRMS Found	Formula Calcd for
104	2,4-bis(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	327.2	327.1452	327.1493	$C_{17}H_{18}N_4O_3$
105	2-amino-4-{[2-(dimethylamino)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	370.27	370.1874	370.1869	$C_{19}H_{23}N_5O_3$
106	2,4-bis{[2-(dimethylamino)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	441.31	441.2609	411.2629	$C_{23}H_{32}N_6O_3$
107	2-amino-4-[(2-aminoethyl)amino]-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	342.22	342.1561	342.1546	$C_{17}H_{19}N_5O_3$
108	2-amino-4-{[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	472.21			$C_{25}H_{21}N_5O_5$
109	2-amino-7,8-dimethoxy-4-[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	396.32	396.203	396.2061	$C_{21}H_{25}N_5O_3$
110	7,8-dimethoxy-2,4-bis[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	493.44			$C_{27}H_{36}N_6O_3$
111	2,4-bis(glycinyl)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	415.33			$C_{19}H_{18}N_4O_7$
112	*N*-(2-amino-3-cyano-7,8-dimethoxy-5H-chromeno[2,3-b]pyridin-4-yl)glycine	357.26	357.1193	357.1818	$C_{17}H_{16}N_4O_5$

Ex. No.	Compound name	m/z (M+H)	HRMS Theor.	HRMS Found	Formula Calcd for
113	7,8-dimethoxy-2,4-bis[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	415.3	415.1976	415.1972	$C_{21}H_{26}N_4O_5$
114	2-amino-7,8-dimethoxy-4-[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	357.25	357.1557	357.2538	$C_{18}H_{20}N_4O_4$
115	2,4-bis(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	411.35	411.2391	411.2391	$C_{23}H_{30}N_4O_3$
116	2-amino-4-(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	355.26	355.1765	355.1763	$C_{19}H_{22}N_4O_3$
117	7,8-dimethoxy-2,4-bis(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	383.31	383.2078	383.2085	$C_{21}H_{26}N_4O_3$
118	2-amino-7,8-dimethoxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	341.25	341.1608	341.1623	$C_{18}H_{20}N_4O_3$
119	2,4-bis(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	355.27	355.1765	355.1784	$C_{19}H_{22}N_4O_3$
120	2-amino-4-(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	327.21	327.1452	327.142	$C_{17}H_{18}N_4O_3$

EXAMPLE 121

[000216] This illustrates the production of 2,4-diamino-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000217] To a stirred solution of 3,4-dimethoxyphenol (35.7mmol, 5.5g) and piperidine (40mmol, 3.4g) in ethanol (50mL) was slowly added formaldehyde (37%, water, 39.5mmol, 3.2g). The mixture was stirred at room temperature for 4 hours and then evaporated *in vacuo* and the

resultant residue was partitioned between ethyl acetate (100mL) and water (100 mL). The organic layer was washed with water, dried ($MgSO_4$) and evaporated to give a colorless oily residue. To a solution of the above oily product in acetone was added methyl iodide (100mmol, 14.2g) and the mixture was stirred at room temperature overnight. The resultant white precipitate was collected by filtration, washed with ether and air-dried to give 8.14 g of a white solid.

[000218] To a slurry of the above solid (1mmol, 390mg) and 2-amino-1-propene-1,1,3-tricarbonitrile (1mmol, 132mg) in ethanol (10mL) was added triethylamine (0.5mL) and the resultant solution was heated at reflux for 30 minutes. After cooling to room temperature, the precipitate was collected by filtration, washed with ethanol and air-dried to give the product as a white solid (178mg, 60% yield). ^{1}H NMR (400 MHZ, DMSO) δ 6.582 (s, 1H), 6.574 (s, 1H), 6.406 (s, 2H), 6.241 (s, 2H), 3.686 (s, 3H), 3.671 (s, 3H), 3.524 (s, 2H); m/z 299 (M+H).

EXAMPLE 122

[000219] This illustrates the production of 2(2,4-diamino-3-cyano-8-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile.

[000220] To a solution of 2-hydroxy-4-methoxybenzaldehyde (10mmol, 1.52g) and malononitrile (40mmol, 2.64g) in ethanol (250mL) was added six drops of piperidine. The mixture was heated at 50°C for 10 minutes and then stirred at room temperature for 5 hours. The resultant precipitate was collected by filtration and recrystallized from methanol to give the product as a pale yellow solid (1.19g, 36% yield). ^{1}H NMR (400 MHz, DMSO) δ 7.274(d, 1H), 6.999 (s, 2H), 6.817 (dd, 1H), 6.733 (d, 1H), 6.619 (s, 2H), 4.804 (d, 1H), 4.734 (d, 1H), 3.757 (s, 3H); m/z 333 (M+H).

EXAMPLE 123

[000221] This illustrates the production of 2(2,4-diamino-3-cyano-7-bromo-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile.

[000222] To a solution of 5-bromo-2-hydroxybenzaldehyde (10mmol, 2g) and malononitrile (35mmol, 2.31g) in ethanol (200mL) was added six drops of piperidine and the mixture was stirred at room temperature for 30

hours. The resultant precipitate was collected by filtration and recrystallized from methanol to give the product as a white solid (1.68g, 44% yield). ^{1}H NMR (400 MHz, DMSO) δ 7.489 (dd, 1H), 7.344 (d, 1H), 7.230 (d, 1H), 7.063 (s, 2H), 6.686 (s, 2H), 4.876 (d, 1H), 4.850 (d, 1H); m/z 381, 383 (M+H).

EXAMPLE 124

[000223] This illustrates the production of 2(2,4-diamino-3-cyano-7-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile.

[000224] To a solution of 2-hydroxy-5-methoxybenzaldehyde (10mmol, 1.52g) and malononitrile (40mmol, 2.64g) in ethanol (350mL) was added six drops of piperidine and the mixture was stirred at room temperature for 18 hours. The resultant precipitate was collected by filtration, successively washed with ethanol and ether and and air-dried to give the product as a grey solid (1.42g, 43% yield). ^{1}H NMR (400 MHz, DMSO) δ 7.107(d, 1H), 6.990 (m, 3H), 6.865 (d, 1H), 6.603 (s, 2H), 4.850 (d, 1H), 4.794 (d, 1H), 3.724 (s, 3H); m/z 333 (M+H).

EXAMPLE 125

[000225] This illustrates the production of 2(2,4-diamino-3-cyano-8-hydroxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile.

[000226] To a solution of 2,4-dihydroxybenzaldehyde (10mmol, 1.38g) and malononitrile (40mmol, 2.64g) in ethanol (350mL) was added six drops of piperidine and the mixture was stirred at room temperature for 5 hours. The resultant precipitate was collected by filtration, washed successively with ethanol and ether and air-dried to give the product as a yellow solid (1.62g, 51% yield). ^{1}H NMR (400 MHz, DMSO) δ 9.887 (s, 1H), 7.162 (d, 1H), 6.971 (s, 2H), 6.613 (dd, 1H), 6.597 (s, 2H), 6.497 (d, 1H), 4.743 (d, 1H), 4.687 (d, 1H); m/z 319 (M+H).

EXAMPLE 126 - 135

[000227] This illustrates the production of certain aminocyanopyridine compounds of the present invention.

[000228] The aminocyanopyridine compounds listed in the table below were produced according to the general method described in Example

123. NMR analysis was carried out for each material according to the method described above. The names and NMR data for each compound is provided in the table.

Ex. No.	Compound name	m/z (M+H)
126	2,4-diamino-7-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	269
127	2(2,4-diamino-3-cyano-7-hydroxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	319
128	2,4-diamino-7-bromo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	317, 319
129	2(2,4-diamino-3-cyano-9-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	333
130	2,4-diamino-5-(2-fluoro-phenyl)-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	363
131	2(2,4-diamino-3-cyano-7-chloro-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	337
132	2,4-diamino-5-phenyl-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	331
133	2,4-diamino-5-(3-fluoro-phenyl)-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	363
134	2,4-diamino-7-bromo-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	347, 349
135	2,4-diamino-5-phenyl-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	345

[000229] All references cited in this specification, including without limitation all papers, publications, patents, patent applications, presentations, texts, reports, manuscripts, brochures, books, internet postings, journal articles, periodicals, and the like, are hereby incorporated by reference into this specification in their entireties. The discussion of the references herein is intended merely to summarize the assertions made by their authors and no admission is made that any reference constitutes prior art. Applicants reserve the right to challenge the accuracy and pertinency of the cited references.

[000230] In view of the above, it will be seen that the several advantages of the invention are achieved and other advantageous results obtained.

[000231] As various changes could be made in the above methods and compositions without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.